(00701)

TITLE OF THE INVENTION

FUSED OXABICYCLIC AMINOALCOHOLS AS NEW SCAFFOLDS FOR COMBINATORIAL LIBRARIES

FIELD OF THE INVENTION

The present invention relates to fused oxabicyclic aminoalcohols and derivatives thereof, to their synthesis, to their use as scaffolds for combinatorial libraries and also as intermediates in the synthesis of pharmacologically active agents.

BACKGROUND OF THE INVENTION

Up to now, the role of carbohydrates in drug discovery has been mainly related to their possible involvement in diseases, to the investigation of related biochemical pathways as well as in the design and synthesis of analogues capable of interfering within said biochemical processes. For example glycosides or modified glycosides can be inhibitors of glycosidase or glycosyl transferase and potentially can block invasive processes or cell adhesion occurring in infectious or inflammatory diseases. Glycosidic mimics of syalic acid can be inhibitors of Influenza Neuraminidase. Small modified oligosaccharides heparin-like can affect cell adhesion or modulate anticoagulant properties. Molecular recognitions eliciting immune response may address the design of synthetic vaccines and glycosyl conjugates, either found by natural substance screening or as synthetic analogues, may have therapeutic activity.

Indeed, the last decade has witnessed new roles of carbohydrate chemistry in the drug discovery process.

The sugar template has been used, in fact, as a tool to generate new drugs, by first mimicking non carbohydrate structures like peptides and, more recently, as structural scaffold bearing pharmacophoric functionalities to be used in combinatorial chemistry approaches.

The conformational rigid structure of carbohydrates, as well as the possibility of their extensive functionalisation, lead to an impressive structural variety of compounds and thus render this carbohydrates class particularly attractive for developing new libraries of compounds with a high degree of diversity. See, for a general reference, S. Borman, C&EN, July 20, 1998, 49-52; M.J. Sofia, et al. J. Org. Chem. 1998, *63*, 2802; H. Kunz, et al. Angew. Chem. Int. Ed. Engl. 1998, *37*, 2503.

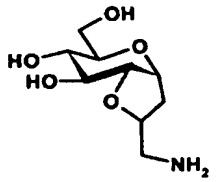
Monosaccharides like hexoses or pentoses, in particular, have structural characteristics that make them very attractive as scaffolds for primary libraries. In fact, apart from being multiply functionalised, they are conformationally rigid or, at least, have a limited conformational freedom.

In addition, by showing a given stereochemical diversity, they can provide a defined three-dimensional spatial arrangement of suitable pharmacophoric substituents. Furthermore, the possible extensive functionalization of the hydroxyl groups in monosaccharides, can generate pharmacophoric diversity and also increase lipophilicity. This latter property may be optimally modulated so as to provide compounds with an improved pharmacokinetic and metabolic profile that nowadays is checked and required at a much earlier stage, in the drug discovery process.

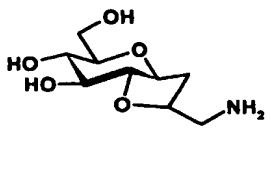
Hence, efforts are addressed to set up efficient methods of selective protection, deprotection and functionalization, either in solution as well as on solid phases, to build up libraries of compounds based on carbohydrate scaffolds.

DETAILED DESCRIPTION OF THE INVENTION

Therefore, it is a first object of the present invention a compound of formula (I) or (II) below



(I)



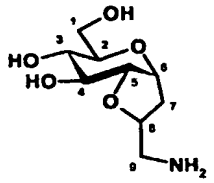
(II)

wherein the hydroxyl groups, each independently, and the amino group, in both formulae (I) or (II) may be optionally protected with suitable hydroxy and/or amino protecting groups; and pharmaceutically acceptable salts thereof.

Non limiting examples of suitable hydroxy protecting groups are, for instance, acyloxy such as acetyloxy, allyloxy, allylcarbonyloxy or arylalkyloxy such as benzyloxy and p.nitrobenzyloxy; preferred hydroxy protecting groups are benzyloxy, p.nitrobenzyloxy and allyloxy.

Non limiting examples of suitable amino protecting groups are, for instance, alkoxycarbonylamino groups such as tert-butoxycarbonylamino (boc-amino) and allyloxycarbonylamino.

For a better understanding of the invention and unless otherwise provided, when referring to the positions of the hydroxyl and amino groups, the numbering system is the one conventionally adopted for these molecules, for instance as reported below for the compound of formula (I):



(I)

In addition, as the compounds of formula (I) and (II) may bear a free amino group, any of the said compounds in the form of an acid addition salt, for instance a pharmaceutically acceptable salt, e.g. hydrochloride, has to be intended as comprised within the scope of the present invention.

As formerly indicated, and with the aim of finding a new tool to improve speed in drug discovery, the above oxabicylic aminoalcohols of formula (I) or (II) may be advantageously used as new scaffolds for combinatorial libraries.

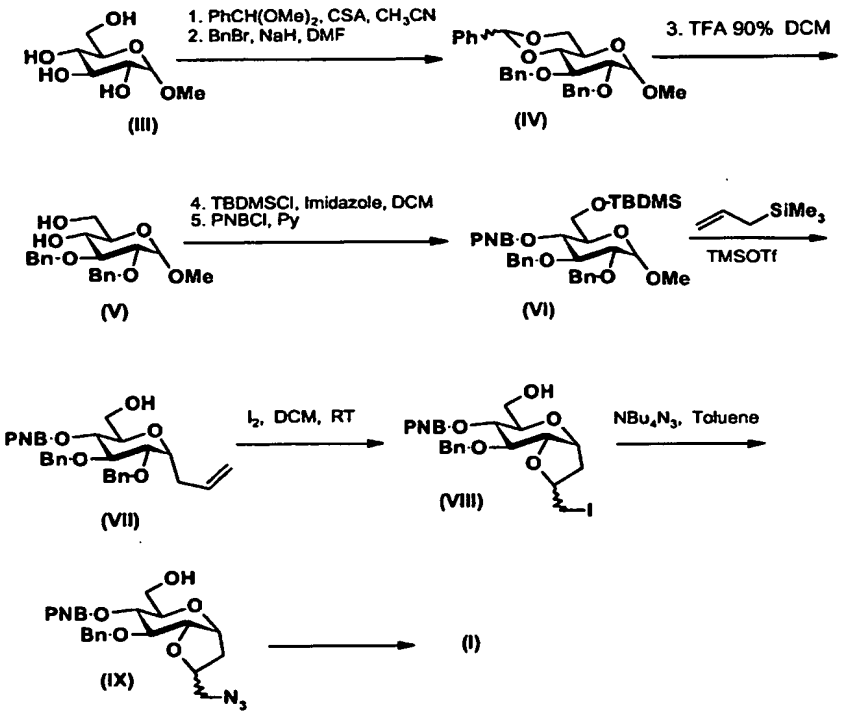
It is well known in the art that a desired property to be improved in an early phase of drug discovery is the so-called drug-like character of a compound, for instance related to its toxicity, solubility, metabolic cleavage and pharmacokinetic properties, in general.

In this respect, it should be clear to the skilled man the importance and usefulness of a non-planar scaffold of formula (I) or (II), being characterized by a high degree of functionalization in a frozen conformation or, at least, with a limited number of possible conformations. Moreover, both scaffolds (I) and (II) may be properly functionalized in a variety of ways, for instance by varying/modulating the nature of the substituents, their relative position and also their spatial direction. In addition, the possibility of having a few polar groups (e.g. hydroxyl and amino groups) that can be easily substituted/functionalized with a wide range of suitable hydrophilic or hydrophobic moieties may contribute even more to modulate the water solubility of the desired compounds so obtained. Furthermore, as these compounds of formula (I) and (II) may be selectively linked to a solid chromatographic support, through any one of the several functional groups, they may be also used in chromatographic techniques.

The compounds of formula (I) and (II), either as such or being protected at any one of the hydroxyl and/or amino groups with well-known protecting agents, may be prepared according to the synthetic processes described below and variants thereof. The said processes for preparing the compounds of formula (I) and (II), together with variants thereof, have all to be intended as a further object of the invention.

For ease of references, please find below synthetic scheme (1) and scheme (2) for preparing the compounds of formula (I), and scheme (3) for preparing the compounds of formula (II).

Scheme 1



Commercially available α-D-glucopyranoside of formula (III) is first reacted with (dimethoxy)methylbenzene in the presence of camphorsulphonic acid (CSA) and in a suitable solvent such as, for instance, acetonitrile. The obtained mixture is then reacted

with benzyl bromide (BnBr) and sodium hydride (NaH) in a suitable solvent, for instance dimethylformamide, so as to obtain the compound of formula (IV).

This latter is then reacted under acidic conditions, for instance with a 90% solution of trifluoroacetic acid in dichloromethane, so as to obtain the compound of formula (V).

The compound of formula (V) may be regarded as a key intermediate derivative, as it can be converted as per instant scheme (1) or, alternatively, according to the subsequent scheme (2).

In the former case, compound (V) is selectively silylated with tert-butyl-dimethylsilyl-chloride (TBDMSCl), in the presence of imidazole and dichloromethane, and the hydroxyl group in position 4 is subsequently protected, for instance with p.nitrobenzylchloride (PNBCl) in the presence of pyridine, so as to yield the compound of formula (VI).

Subsequent reaction with allyltrimethylsilane and trimethylsilyltriflate allows to obtain the compound of formula (VII) which is further reacted with iodine in dichloromethane, at room temperature, so as to promote cyclization to the compound of formula (VIII).

Finally its reaction with tetrabulyammonium azide (NBu_4N_3), in a suitable solvent such as toluene, allows to get the compound of formula (IX) which can be easily converted to the derivative of formula (I) wherein all of the hydroxyl groups are not protected and the azido group is replaced by amino, by working according to conventional methods.

The above conversion may be thus carried out under reductive conditions, for instance through catalytic hydrogenation in the presence of platinum or palladium catalysts, in the presence of acetic acid and lower alcohols, for instance acetic acid/methanol mixtures.

Likewise, azide reduction may be also accomplished under chemical reductive conditions, for instance with tin(II) chloride in the presence of thiophenol and triethylamine.

Additionally, p.nitrobenzyl deprotection may also occur with sodium methoxide in tetrahydrofuran/methanol mixtures.

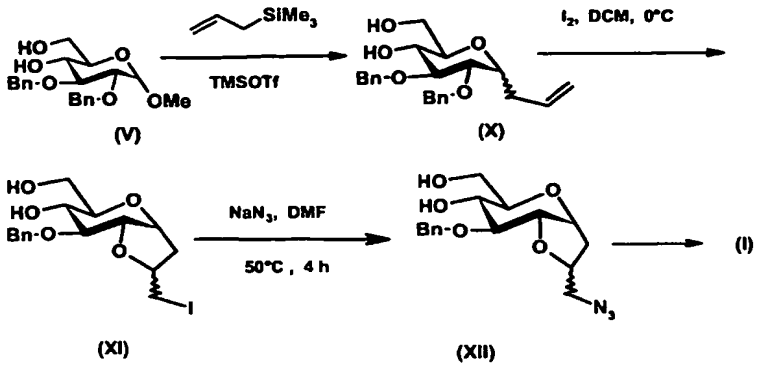
For a better understanding of any meaning intended for the functional/protecting groups and of the reactants being identified in scheme (1), as well as in any other part of the present specification, herewith below is a list of groups being conveniently indicated with their coding system.

List of abbreviations:

Alloc	allyloxycarbonyl
Bn	benzyl
BSTFA	N,O-bis(trimethylsilyl)trifluoroacetamide
CSA	Camphosulfonic acid
DCM	dichloromethane
DIC	N,N'-diisopropylcarbodiimid
DIPEA	N-ethyldiisopropylamine
DMAP	4-dimethylaminopyridine
DMF	N,N'-dimethylformamide
HATU	[*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate]
HOBt	hydroxybenzotriazole
KHMDS	potassium hexamethyldisylazide
Me	methyl
Ph	phenyl
PNB	*para*nitrobenzoyl
PTSA	*para*toluenesulfonic acid
TBDMS	tertbutyl-dimethyl-silyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	*tetra*hydrofuran
TMOF	trimethyl orthoformate

As formerly reported, the intermediate compound of formula (V) being prepared in scheme (1) may be also conveniently reacted according to the following synthetic scheme (2).

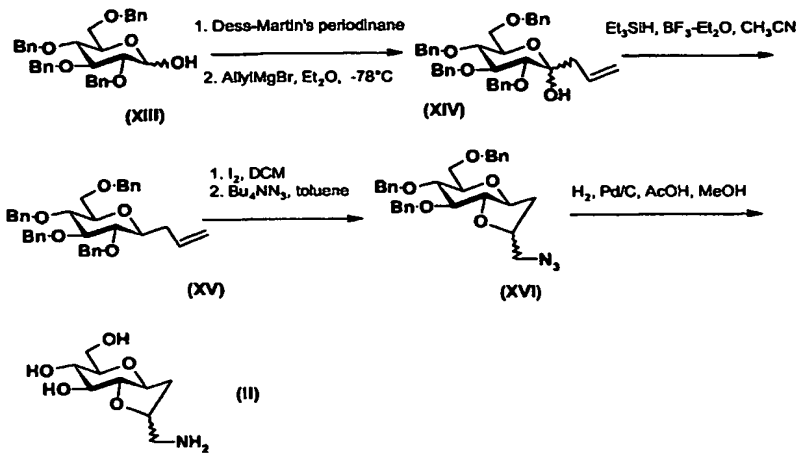
Scheme 2



From the above, it is evident that the reactions of scheme (2) are essentially those of scheme (1), being carried out on a different intermediate. In this specific case, however, the compound of formula (X) is present, in its prevalent α-configuration at the anomeric center, hence enabling cyclization to the compound of formula (XI) at low temperature. The iodo derivative of formula (XI) is then converted to the compound of formula (XII) through reaction with sodium azide. This latter derivative, as in the previous case, may be converted to the corresponding compound bearing free hydroxyl groups and wherein the azido group is replaced by amino, for instance through catalytic hydrogenation or chemical reduction. This synthetic strategy can be convenient because of the successive new process we set up for linking the substrate to a proper solid support through the primary hydroxyl group with regioselectivity.

Finally, the compounds of formula (II) may be prepared according to the process, still comprised within the scope of the present invention, as per synthetic scheme (3) below.

Scheme 3



The process of scheme (3) starts from the known compound of formula (XIII) and, through a different synthetic strategy, gives the key intermediate XV (β–anomer) that allows to obtain the desired compound of formula (II), by reacting the several intermediates, essentially as set forth in previous schemes (1) and (2).

More in particular, the compound of formula (XIII) is first reacted with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benzodioxol-3(1H)-one (Dess-Martin periodinane) so as to obtain an intermediate carbonyl derivative which may be further reacted, without being isolated, with allylmagnesium bromide.

This latter reaction is carried out in a suitable solvent, for instance diethyl ether, at -78°C, so as to get the compound of formula (XIV).

According to an alternative synthetic approach, the compound of formula (XIII) may be also oxidized with other well-known oxidative agents comprising, for instance, the reaction with dimethylsulfoxide (DMSO) and acetic anhydride, so as to get the intermediate carbonyl derivative further reacted with allylmagnesium bromide, as set forth above.

The compound of formula (XIV) is then converted into the derivative of formula (XV) by reaction with triethylsilane (Et_3SiH) and boron trifluoride in diethyl ether (BF_3-Et_2O), in the presence of a suitable solvent such as acetonitrile.

The compound (XV) is then converted into the compound of formula (II), substantially as formerly reported in scheme (1), through reaction with iodine in dichloromethane carried out at room temperature or even higher temperature, e.g. up to refluxing temperature, and subsequent reaction with tetrabutylammonium azide. Catalytic hydrogenation, or anyway deprotective reduction of this latter, easily allows to obtain the compound of formula (II) with free hydroxyl groups, which is further susceptible of being functionalized/protected in a variety of ways and according to conventional methods, at any one of the hydroxy and/or amino groups.

For a more detailed explanation of the processes for preparing the compounds of formula (I) and (II) according to the invention, as set forth in schemes from (1) to (3) and variants thereof, see the experimental section.

From all of the above, it is worth noting that, apart from being converted into a derivative of formula (I) or (II), the compounds of formula (IX), (XII) and (XVI) of schemes (1) to (3), may be also loaded onto a suitable inert polymeric support, and further reacted to give a variety of derivatives. Likewise, any suitable intermediate compound of schemes (1) to (3) and which is susceptible of being anchored onto a polymeric support, may be converted as well into a variety of derivatives.

The above features are described, in details, in a subsequent embodiment of the invention concerning combinatorial libraries of compounds.

In fact, as formerly indicated, the above scaffolds of formula (I) and (II) or, whenever appropriate any synthetic intermediate in the preparation of the compounds of formula (I) and (II), may be properly functionalized - either in solution as well as under solid phase synthesis (SPS) conditions - to give rise to libraries of compounds.

In this respect it is worth pointing out that by choosing the most suitable synthetic scheme, it is possible to selectively protect/deprotect given hydroxyl groups so as to give rise to a variety of compounds.

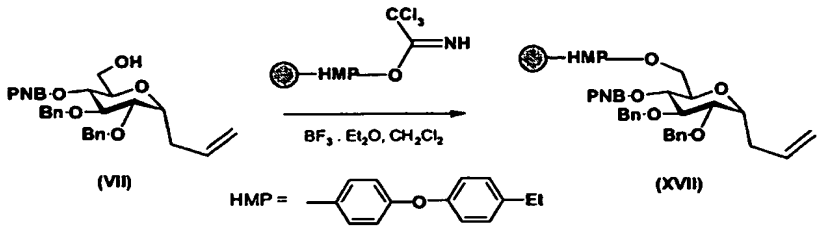
Just as an example, the compound of formula (IX), in scheme (1), may be properly anchored to a solid support resin through its available hydroxyl group in position 6.

As such, the obtained supported compound can be then reacted according to well known combinatorial chemistry techniques, for instance by working under solid phase synthesis (SPS) conditions.

Preferably, the above resin is a commercially available polystyrenic resin optionally properly functionalized according to known methods and may include, for instance, Wang resin, Trityl resin, Cl-trityl resin, Rink amide resin, Tentagel OH resin and derivatives thereof.

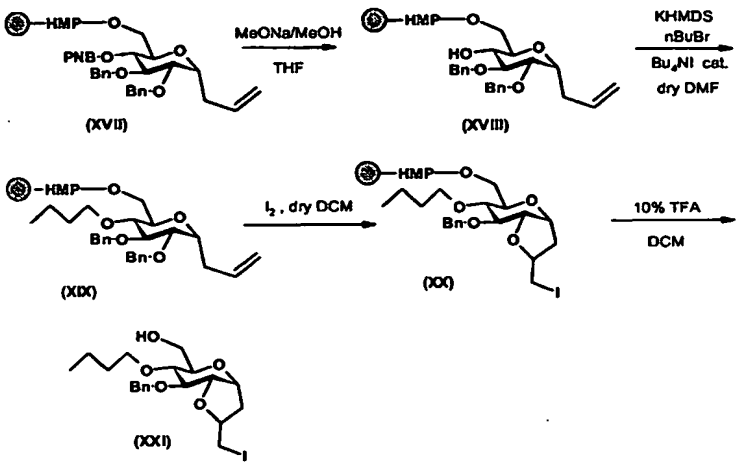
For a better understanding, here below are additional synthetic schemes from (4) to (8) which illustrate, as non limiting examples, the possibility of linking a given scaffold of formula (I) or (II) to a suitable resin, e.g. Wang trichloroacetimidate resin.

Scheme 4: loading of compound (VII) onto a polymeric support



As reported in scheme (4), the allyl derivative of formula (VII) is loaded onto a polymeric support through its primary hydroxyl group, being covalently bonded to the HMP Wang resin itself. The polymer supported compounds (XVII) thus obtained may be further reacted in a variety of ways, for instance as reported below in scheme 5:

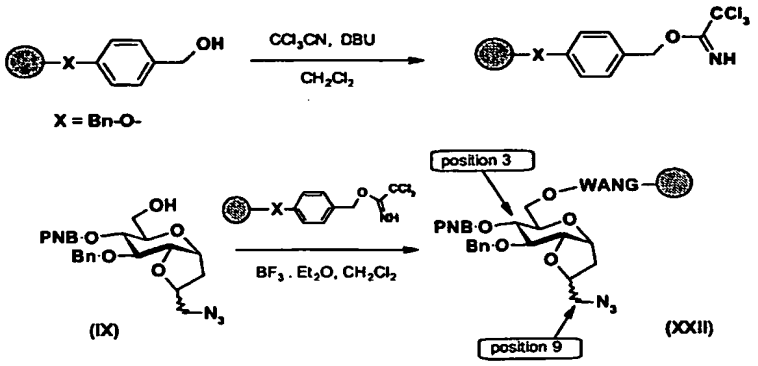
scheme 5



In fact the resin-bound C-glycoside (XVII) can be deprotected at position 4 and the free hydroxyl group can give a variety of ethers like n.butylether as shown in the scheme, as an example. The allyl group in C-1 can undergo cyclization on solid phase to the bicyclic iododerivative (XX) that can be further modified to azidoderivative, analogously to the conversions of (XI) to (XII) or of (XV) to (XVI), or cleaved from the resin to give (XXI). This compound is a scaffold orthogonally substituted that can undergo further introduction of diversity, independently, at the primary hydroxyl group, at the benzylated oxygen atom and at the iodomethyl moiety.

Loading on a resin can be performed at the level of the bicyclic azido derivative (IX).

Scheme 6: loading of the azide (IX) of scheme (1) onto a polymeric support



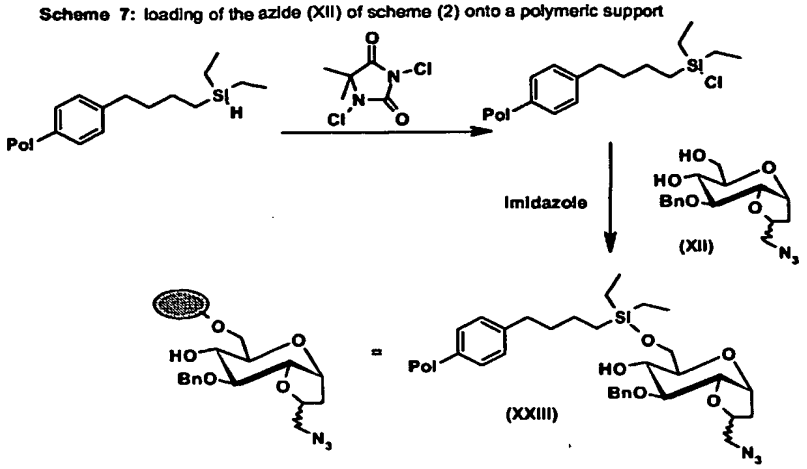
As reported in scheme (6), the resin wherein X stands for benzyloxy is first functionalized at the hydroxyl moicty with trichloroacetonitrile and 1,8-diaza-7-bicyclo[5.4.0]undecene (DBU), in a suitable solvent such as dichloromethane, and then reacted with the given azidoderivative of the scaffold (I), so as to get a polymer supported form of it (XXII).

In this respect, it is worth noting that the polymer loaded derivative of the scaffold (I) being so prepared, may be used in combinatorial chemistry approaches, by preparing libraries of compounds wherein diversity may occur, either selectively in positions 3 or 9 or, alternatively, in both of said sites.

Alternatively, the compound of formula (XII) of scheme (2) can be selectively linked to a resin, through its primary hydroxyl group, so as to leave the secondary hydroxyl group available for combinatorial functionalization.

Please find below, as an example, synthetic scheme (7) wherein the proper derivative of scaffold (I) is regioselectively loaded to the polymeric supporting resin.

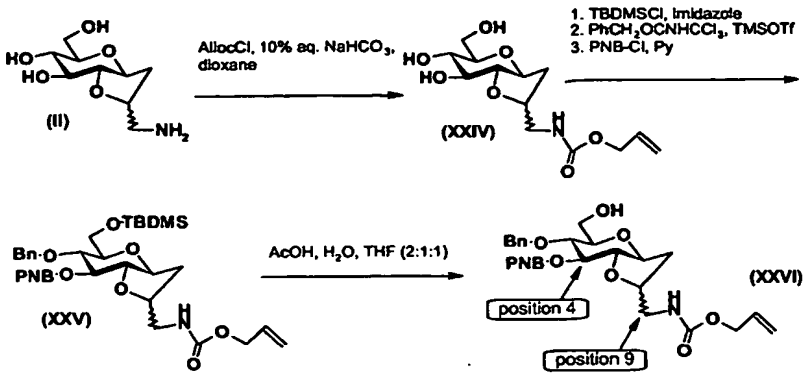
Scheme 7: loading of the azide (XII) of scheme (2) onto a polymeric support



At first, according to scheme (7), the resin-bound silyl chloride is generated in situ by properly reacting a polymer supported silane resin with 1,3-dichloro-5,5-dimethylhydantoin. The reaction can be easily monitored through IR detection, by checking the complete absence of the Si-H bond stretch at 2094 cm^{-1}. Then, reaction with scaffold (I) of scheme (2) allows to regioselectively support it on the polymer, in position 6 (e.g. at the primary hydroxyl group), so as to give rise to (XXIII). Again, the supported C-glycoside (XXIII) has the appropriate substitution pattern by which 3-OH, 4-OH, and azido/amino group can be independently modified to generate a compound library.

Analogous considerations also apply to scaffold (II) which has the opposite stereochemistry at the anomeric carbon atom. In this case the best synthetic strategy leads to an unprotected scaffold (II) that requires a process of proper orthogonal protection at the amino group and the secondary hydroxyl groups [see synthetic scheme (8) below] before loading intermediate (XXVI) onto a resin through its primary hydroxyl group.

Scheme 8: functionalization of the amine (II)



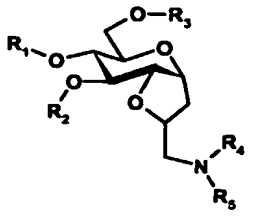
In scheme (8), the starting compound of formula (II) is thus reacted with allyloxycarbonyl chloride (AllocCl), under basic conditions and in the presence of dioxane. The derivative (XXIV) so obtained is then reacted with tert-butyl-dimethylsilyl chloride and imidazole, with benzyl trichloroacetimidate ($PhCH_2OCNHCCl_3$) and then with p.nitrobenzyl chloride in pyridine, so as to get a bicyclic compound (XXV) which is finally hydrolyzed, for instance with aqueous acetic acid in tetrahydrofuran, to get the final compound (XXVI).

Interestingly, the two positions amenable to parallel functionalization are position 4 at the sugar skeleton and position 9 at the fused tetrahydrofuran ring.

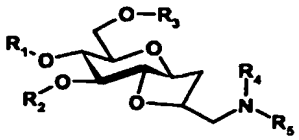
In addition, as the intermediate compound has functional groups which are protected in the so-called orthogonal way, these same groups may be selectively removed through conventional methods. Therefore, compound (XXV) as well as compound (XXVI) can be used to generate a library of compounds either in solution or on solid phase. In fact, the bicyclic compound (XXVI) can be loaded onto a resin through its free primary hydroxyl group (1-OH) analogously to what is described in scheme (6) for the derivatives of scaffold (I).

As formerly indicated, the above scaffolds (I) and (II) and any intermediate derivative thereof may be thus used for preparing combinatorial libraries of compounds.

Therefore, it is a further object of the present invention a library of two or more compounds of formula (XXVII) or of formula (XXVIII)



(XXVII)



(XXVIII)

wherein

R_1, R_2 and R_3 are, the same or different and independently from each other, a hydrogen atom or a group of formula (XXIX)

$$-X-R_6 \quad \text{(XXIX)}$$

wherein X is a single bond or a divalent group selected from -CO-, -CS-, -CONR'- or -CSNR'-;

R' and R_6 are, the same or different and independently in each occasion, a hydrogen atom or an optionally substituted group selected from:

a) straight or branched C_1-C_8 alkyl;

b) C_3-C_6 cycloalkyl or C_3-C_6 cycloalkyl-alkyl;

c) aryl or arylalkyl;

d) heterocyclyl or heterocyclylalkyl;

or R' and R_6, taken together with the nitrogen atom to which they are attached, form an optionally substituted 5 to 7 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from N, NH, O or S; or alternatively, any one of R_1 and R_2 or R_1 and R_3 may be linked together so as to form a 5 to 7 membered heterocycle comprising two oxygen atoms, through an alkylene chain $-(CH_2)_m-$ wherein m is an integer from 1 to 3;

R_4 and R_5 are, the same or different and independently from each other, a hydrogen atom or a group of formula (XXX)

$$-Y-R_6 \quad \text{(XXX)}$$

wherein Y is a single bond or a divalent group selected from -CO-, -CS-, $-SO_2-$, -CONR'-, -CSNR'- or -COO-;

R' and R_6, the same or different and independently in each occasion, are as above defined or, alternatively

R_4 and R_5, taken together with the nitrogen atom to which they are attached, form an optionally substituted 5 to 7 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from N, NH, O or S;
and pharmaceutically acceptable salts thereof.

The compounds of formula (XXVII) or (XXVIII) of the invention have asymmetric carbon atoms and may therefore exist as individual optical isomers, as racemic admixtures or as any other admixture comprising a majority of one of the two optical isomers, which are all to be intended as within the scope of the present invention.

In the present description, unless otherwise specified, with the term straight or branched C_1-C_8 alkyl we intend any of the groups such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

With the term C_3-C_6 cyclo alkyl we intend, unless otherwise provided, a cycloaliphatic ring such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term aryl includes carbocyclic or heterocyclic hydrocarbons with from 1 to 2 ring moieties, either fused or linked to each other by single bonds, wherein at least one of the rings is aromatic; if present, any aromatic heterocyclic hydrocarbon also referred to as heteroaryl group, comprises a 5 to 6 membered ring with from 1 to 3 heteroatoms or heteroatomic groups selected among N, NH, O or S.

Examples of aryl groups according to the invention are, for instance, phenyl, biphenyl, α- or β-naphthyl, dihydronaphthyl, thienyl, benzothienyl, furyl, benzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, purinyl, quinolyl, isoquinolyl, dihydroquinolinyl, quinoxalinyl, benzodioxolyl, indanyl, indenyl, triazolyl, and the like.

Unless otherwise specified, the term heterocyclyl includes 5 to 6 membered saturated, partly unsaturated or fully unsaturated heterocycles with from 1 to 3 heteroatoms or heteroatomic groups selected among N, NH, O or S.

Apart from the fully unsaturated heterocycles, previously referred to as aromatic heterocycles and encompassed by the term aryl, examples of saturated or partly unsaturated heterocycles according to the invention are, for instance, pyran, pyrrolidine, pyrroline, imidazoline, imidazolidine, pyrazolidine, pyrazoline, thiazoline, thiazolidine,

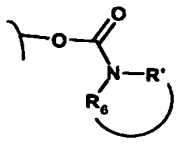
dihydrofuran, tetrahydrofuran, 1,3-dioxolane, piperidine, piperazine, morpholine and the like.

When referring to the libraries of compounds of the invention wherein the group (XXIX) is other than a hydrogen atom, e.g. when X is other than a single bond and R_6 is other than hydrogen, functionalized derivatives such as carboxy, thiocarboxy, carbamate or thiocarbamate compounds are therein disclosed.

Likewise, when referring to the libraries of compounds of the invention wherein the group (XXX) is other than a hydrogen atom, e.g. when Y is other than a single bond and R_6 is other than hydrogen, functionalized derivatives such as carboxamide, thiocarboxamide, sulfonamide, ureido, thioureido or carbamate compounds are therein disclosed.

Unless otherwise provided in the present description, when R' and R_6, being part of any one of the groups of formula (XXIX) or (XXX), are taken together with the nitrogen atom to which they are attached, heterocyclic groups of from 5 to 7 members are formed.

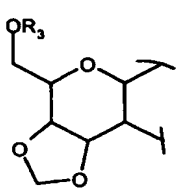
Just as an example, not to be intended as limiting the scope of the invention, when in the group of formula (XXIX) X is -CONR'-, R_6 may be linked to R' so as to give rise to the aforementioned heterocycle, substantially as follows:



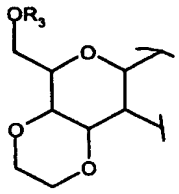
It is also clear to the skilled person that analogous considerations also apply when referring to the group of formula (XXX) or wherein the 5 to 7 membered heterocycle is defined by means of groups R_4 and R_5 linked together through the nitrogen atom to which they are attached.

In addition to the above, 5 to 7 memebered heterocycles comprising two oxygen atoms may be also formed when R_1 and R_2 or R_1 and R_3 are linked together through the aforementioned alkylene chain.

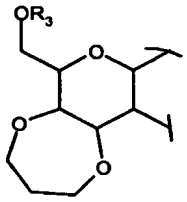
Depending upon the length of the alkylene chain and of the R groups so linked, the following compounds can be thus identified:



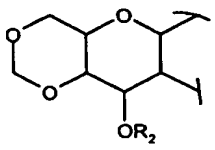
m = 1



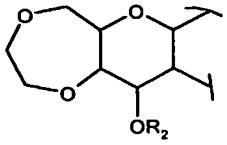
m = 2



m = 3



m = 1



m = 2

According to the present invention and unless otherwise provided, any of the above R' and R_6 groups, in each occasion, may be optionally substituted, in any of their free positions, by one or more groups, for instance 1 to 6 groups, independently selected from: halogen, nitro, oxo groups (=O), cyano, alkyl, perfluorinated alkyl, perfluorinated alkoxy, alkenyl, alkynyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl, cycloalkyl, hydroxy, alkoxy, aryloxy, heterocyclyloxy, methylenedioxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy, alkylideneaminooxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, amino, ureido, alkylamino, dialkylamino, arylamino, diarylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, alkoxycarbonylamino, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylthio and alkylthio.

In this respect, with the term halogen atom we intend a fluorine, chlorine, bromine or iodine atom.

With the term alkenyl or alkynyl we intend any of the aforementioned straight or branched C_2-C_6 alkyl groups further bearing a double or triple bond. Non limiting

examples of alkenyl or alkynyl groups of the invention are, for instance, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 1-hexenyl, ethynyl, 2-propynyl, 4-pentynyl, and the like.

With the term perfluorinated alkyl or alkoxy we intend any of the above straight or branched C_1-C_6 alkyl or alkoxy groups which are substituted by more than one fluorine atom such as, for instance, trifluoromethyl, trifluoroethyl, 1,1,1,3,3,3-hexafluoropropyl, trifluoromethoxy and the like.

With the term alkoxy, aryloxy, heterocyclyloxy and derivatives thereof we intend any of the above alkyl, aryl or heterocyclyl groups linked to the rest of the molecule through a oxygen atom (-O-).

From all of the above, it is clear to the skilled person that any group which name is a composite name such as, for instance cycloalkylalkyl, arylalkyl, heterocyclylalkyl, alkoxy, alkylthio, aryloxy, arylalkyloxy, alkylcarbonyloxy, arylalkyl, heterocyclylalkyl and the like, have to be intended as conventionally construed by the parts from which they derive. As an example, a group such as heterocyclylalkyl has to be intended as n alkyl group further substituted by a heterocyclic moiety, wherein alkyl and heterocyclyl are as above defined.

Pharmaceutically acceptable salts of the compounds of formula (XXVII) and (XXVIII) include the acid addition salts with inorganic or organic acids, e.g., nitric, hydrochloric, hydrobromic, sulfuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g., alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine, piperidine and the like.

According to an embodiment of the invention, within the above libraries of formula (XXVII) and (XXVIII), any the above optionally substituted R' and R_6 groups is, at each occurrence, preferably selected from:

- alkyl, e.g. ethyl; isopropyl; n-heptyl; n-butyl; methoxymethyl; dimethylaminomethyl;
- arylalkyl, e.g. benzyl; 2-phenylethyl; α-napthylmethyl; p.methoxyphenylmethyl;

- aryl, e.g. phenyl; 3,5-dimethoxyphenyl; p.methylphenyl; p.fluorophenyl; m.fluoromethyl; m.methoxyphenyl; pyridyl-3-yl; thienyl-2-yl; or
-cycloalkyl, e.g. cyclopropyl.

The above libraries of formula (XXVII) or (XXVIII) can be random libraries, wherein diversity is the main goal to achieve and which may allow biological screening of several compounds, for instance from corporate collections. As an example, random libraries can be built around a non-interactive scaffold through generation of structural diversity, for instance by varying the nature of the attached moieties and/or their mutual position and directionality.

Alternatively, the so called focused libraries may be used for hit expansion or lead optimization. They may be construed by building diversity around a given bond, around a scaffold producing active interactions or even by building pharmacophoric arrays of interactive moieties around a supporting scaffold with variability of their relative positions and spatial directions.

Both the above types of libraries may comprise several compounds being prepared in a combinatorial fashion to afford mixtures which can be tested in biological/pharmaceutical screenings, in high-through-put screenings, as part of a drug discovery program.

Just as an example, when libraries of compounds of formula (XXVII) or (XXVIII) are tested in biological assays, screenings could be performed to evaluate whether one or more of the compounds of the library may exert the desired biological properties.

See, for a general reference to libraries of compounds and uses thereof as tools for screening biological activities, J. Med. Chem. 1999, 42, 2373-2382; and Bioorg. Med. Chem. Lett. 10 (2000), 223-226.

As an example, once a library of compounds of formula (XXVII) or (XXVIII) is thus prepared, for instance consisting of a few hundreds of derivatives, the said library can be very advantageously used for screening towards given protein kinases, and possibly identify protein kinase inhibitors which may be useful, in therapy, in the treatment of diseases associated with protein kinase disregulation or malfunctioning, e.g. tumors.

In this field, the said compounds could be tested as cyclin-dependent kinase inhibitors, for instance cdk2 inhibitors, or as inhibitors of other protein kinases including, for instance, protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2,

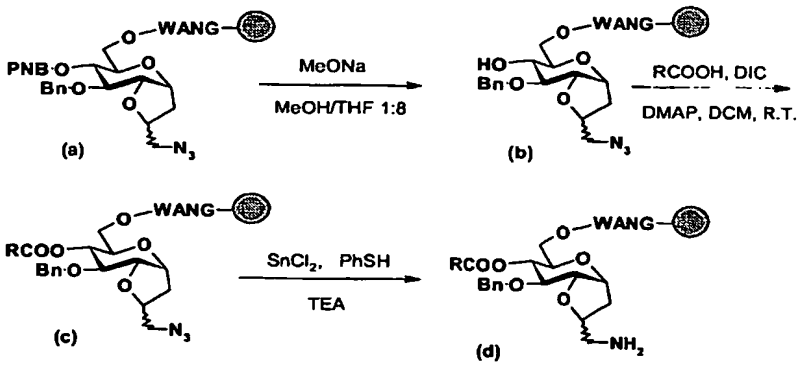
DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, PI3K, weel kinase, Src, Abl, Akt, MAPK, ILK, MK-2, IKK-2, Cdc7, Nek, and the like.

Likewise, these compounds could be also useful as inhibitors of other target proteins like polymerases or proteases of pathological agents, for instance viral or bacterial pathogens.

The preparation of the libraries of formula (XXVII) and (XXVIII) may be carried out according to a variety of alternative processes, all characterized by the fact that given scaffolds of formula (I) and (II) and suitable precursors thereof, optionally supported onto a polymeric resin, may be functionalized, selectively at predefined positions, with several groups.

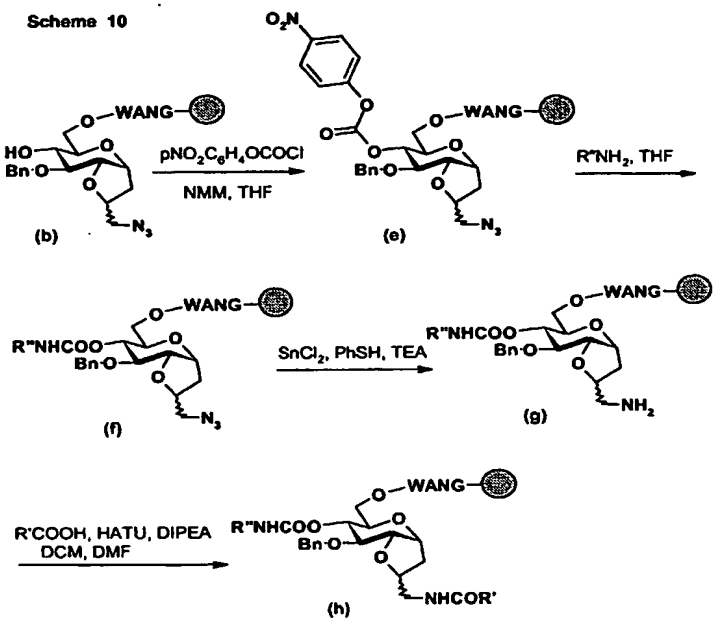
As an example, the solid supported scaffold (I) may be functionalized as reported in the following schemes.

Scheme 9



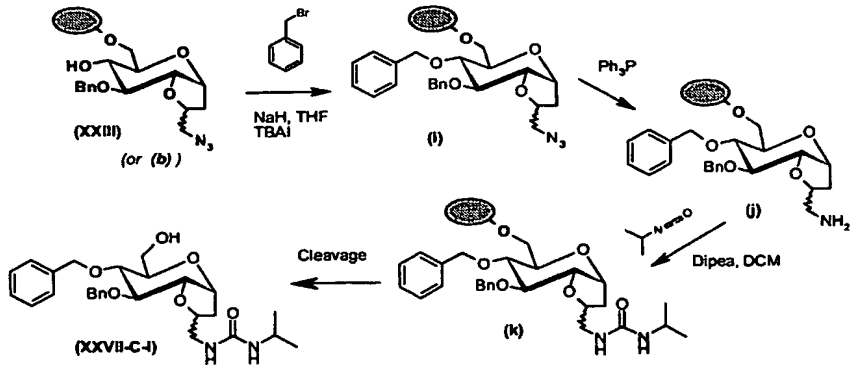
According to scheme (9), the polymer supported scaffold of formula (I) and therein identified as compound (a) is first deprotected at position 3, with sodium methylate in the presence of a methanol/tetrahydrofuran mixture, and subsequently reacted with a suitable carboxylic acid RCOOH, in the presence of N,N'-diisopropylcarbodiimide-4-dimethylaminopyridine (DIC-DMAP), in dichloromethane and at room temperature. The compound (c) thus obtained is then reduced as formerly reported, for instance with tin(II) chloride and thiophenol, in the presence of triethylamine.

Scheme 10



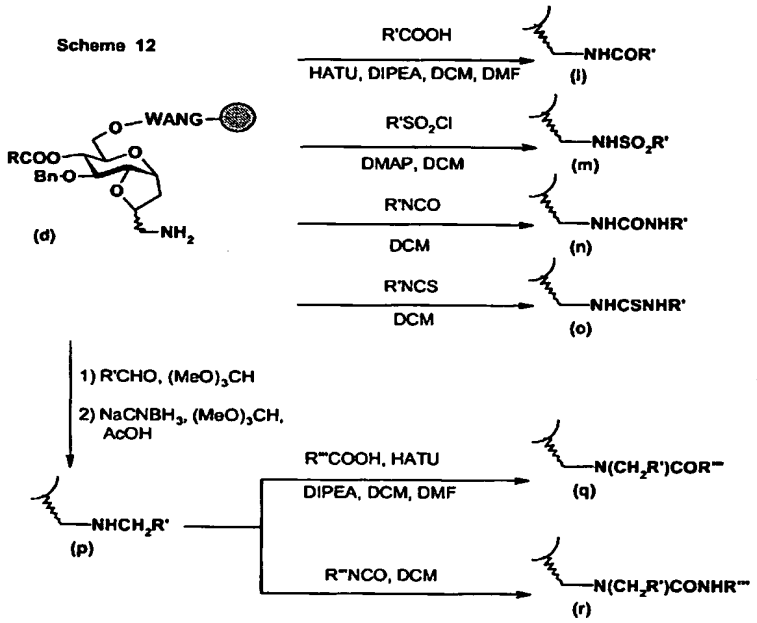
According to scheme (10), the polymer supported compound (b) of scheme (9) may be converted into the corresponding p.nitrophenylcarbonate (e) by means of 4-nitrophenyl-oxycarbonylchloride and N-methylmorpholine (NMM), in tetrahydrofuran. Subsequent aminolysis with $R''NH_2$ followed by azido group reduction to amino (g) and further acylation with R'COOH, yields the carbamate (h).

Scheme 11: Ether formation on solid phase.



According to scheme (11) the polymer supported compound (XXIII) of scheme (7) or (b) of scheme (9) may be converted into a corresponding ether for example benzyl ether and the amino group can be further modified, alkylated, acylated, or converted to an ureido derivative, for instance as per the above scheme.

Scheme 12



According to scheme (12), the polymer supported compound (d) of scheme (9) may be also converted into a variety of derivatives, by properly reacting and functionalizing the amino group, to the corresponding amido derivative of formula (l), sulfonamido derivative of formula (m), ureido derivative of formula (n) or thioureido derivative of formula (o), and the like. In addition, compound (e) may also undergo reductive amination to the corresponding secondary amines (p) which can be further converted into the N,N-disubstituted amides (q) or to the N,N-disubstituted-ureido derivatives (r). All of the above reactions are carried out according to well known methods in the art.

As an example, amides or sulfonamides (l) and (m) may be obtained by reacting (d) with a suitable carboxylic acid R'COOH or sulfonyl chloride $R'SO_2Cl$, in the presence

of condensing agents, e.g. 4-dimethylaminopyridine (DMAP), and in a suitable solvent, e.g. dichloromethane.

Ureido or thioureido derivatives (n) or (o) may be obtained by reacting (d) with a suitable isocyanate or isothiocyanate derivative R'NCO or R'NCS, respectively, in a suitable solvent like dichloromethane.

Reductive amination of (d) to (p) is also accomplished according to conventional techniques, by first reacting the amine (d) with an aldehyde derivative R'CHO and by subsequently reducing the amido group thus formed, with sodium cyanoborohydride.

Interestingly, the methylamino derivative (p) thus obtained may be further functionalized through reaction with a suitable carboxylic acid R'''COOH to yield N,N-disubstituted amides (q) or, alternatively, through reaction with an isocyanate R'''NCO to the corresponding ureido compound (r).

From all of the above reaction schemes, it is clear to the skilled man that the nature of any reactant being employed and, more particularly, the kind of R, R', R'' or R''' substituent, will determine the substitution/functionalization in position 3 and/or at the amino group, as set forth in formula (XXVII).

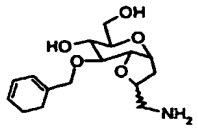
In addition, it is also clear that when preparing the compounds of formula (XXVII) or (XXVIII) according to any one of the aforementioned process variants, optional functional groups within the starting materials or the intermediates thereof and which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques. Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

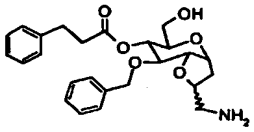
The resulting compounds are then subsequently cleaved from the resin to which they are linked according to known methods, for instance under acidic conditions, e.g. in the presence of trifluoroacetic acid in dichloromethane; detachment from the resin lead to the corresponding free hydroxymethyl derivatives as final compounds.

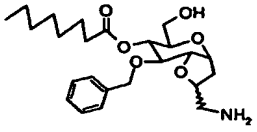
As reported in the following experimental section, the purity of the compounds thus prepared was assessed by ^{1}H NMR spectroscopy of the crude reaction mixtures. Flash chromatography gave the pure target compounds which were fully characterized by ^{1}H-NMR, MS or EA (elemental analysis).

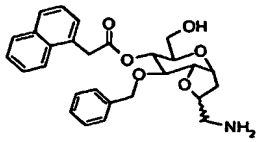
As an example, the following amines, amides and ureido derivatives of formula (XXVII), as per charts A, B and C, were thus prepared.

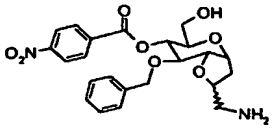
Chart A - amines herewith conveniently indicated with formula (XXVII-A-)

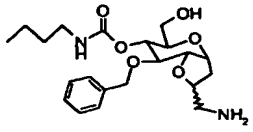

(XXVII-A-a)

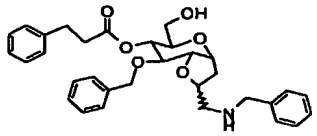

(XXVII-A-b)


(XXVII-A-c)


(XXVII-A-d)


(XXVII-A-e)


(XXVII-A-f)


(XXVII-A-g)

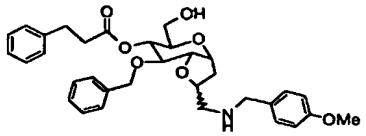
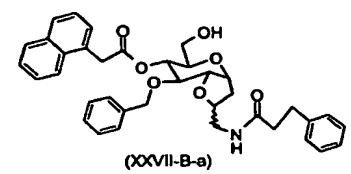
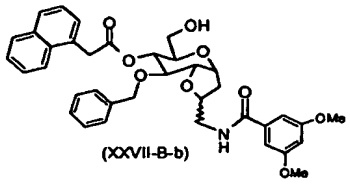
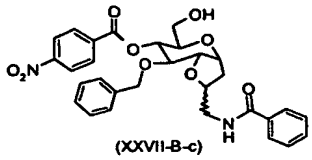
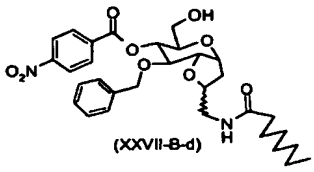

(XXVII-A-h)

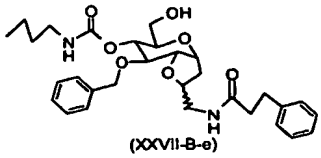
Chart B - amides herewith conveniently indicated with formula (XXVII-B-)

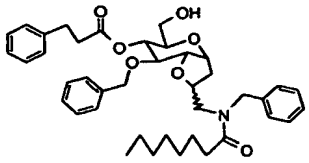

(XXVII-B-a)

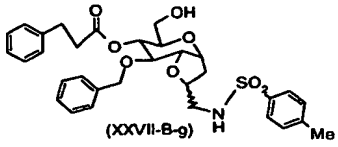

(XXVII-B-b)

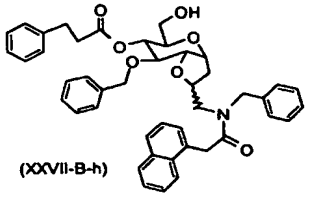

(XXVII-B-c)

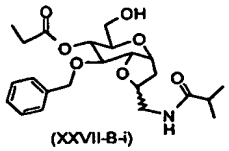

(XXVII-B-d)


(XXVII-B-e)


(XXVII-B-f)


(XXVII-B-g)


(XXVII-B-h)


(XXVII-B-i)

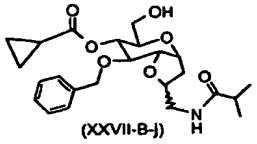

(XXVII-B-j)

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Chart B cont. - amides herewith conveniently indicated with formula (XXVII-B-)

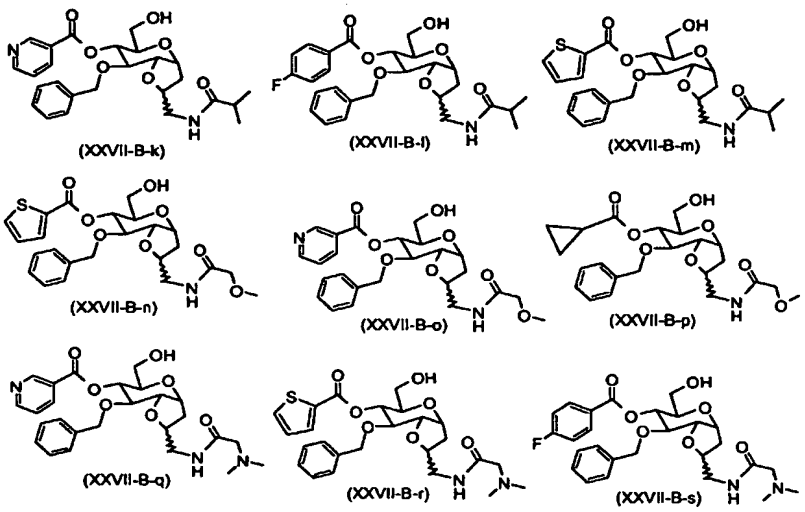


Chart C - ureido derivatives herewith conveniently indicated with formula (XXVII-C-)

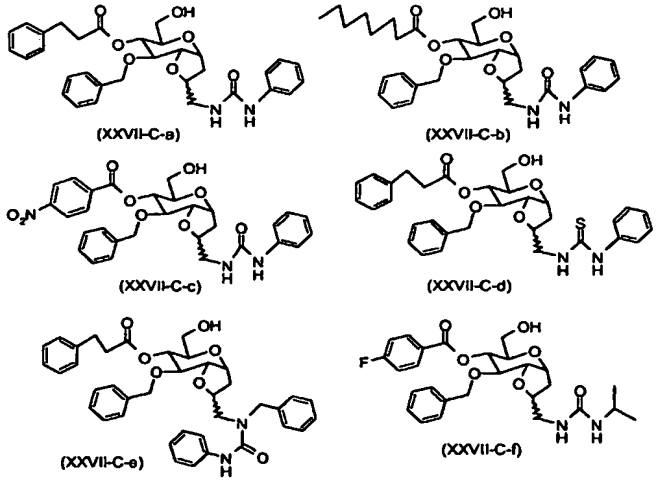
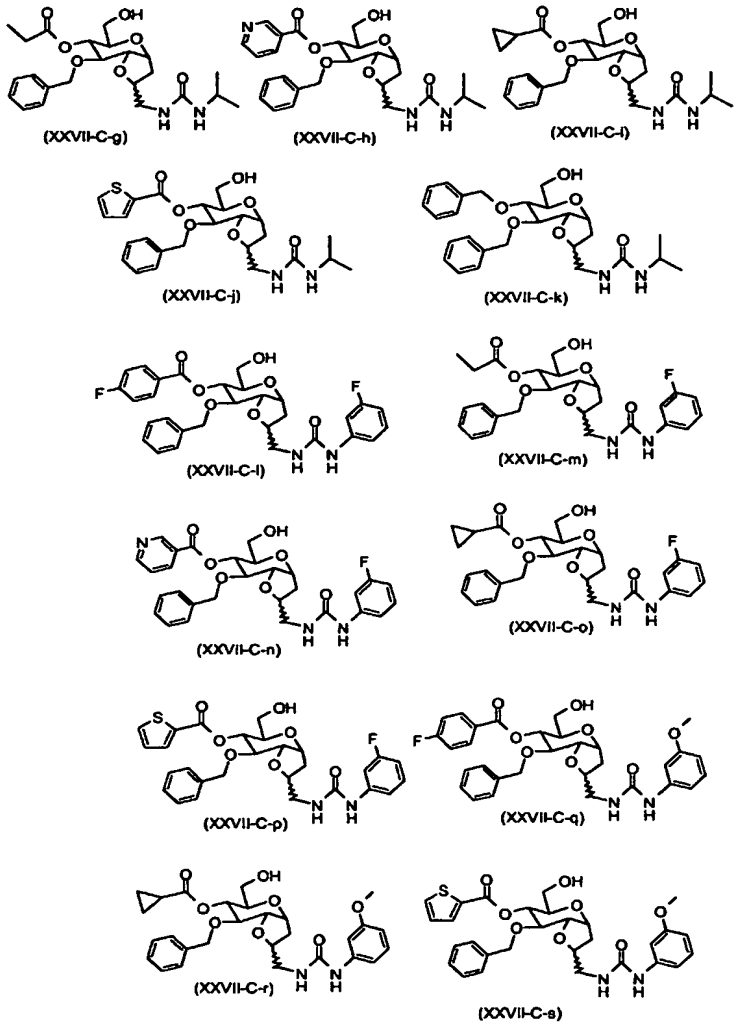


Chart C cont. - ureido derivatives herewith conveniently indicated with formula (XXVII-C-)



5

Each of these compounds, alternatively, can be also singly prepared, in a pure form, for screening, further testing or for use as a medicament. Said pure compounds, or mixtures thereof, may also be appended to a solid support, either directly or through a tether, or incorporated into polymers or gels to afford novel substances that could have utility in the fields of separation science, in the development of diagnostic materials or exhibit utility as affinity chromatographic supports.

With the aim of better illustrate the present invention, without posing any limitation to it, the following examples are now given.

EXAMPLES

Compounds (IV), (V), and the related intermediates were obtained from the commercially available methyl α-D-glucopyranoside as shown in scheme (1) following published procedures for the synthetic transformations [1) M.E. Evans *Carbohydr. Res.* **1971**, *21*, 473-475; 2) D.J. Bell and J. Lorber *J. Chem. Soc.* **1940**, 453-455; and 3) Ishikawa and Fletcher *J. Org. Chem.* **1969**, *34*, 563]. Characterization of compounds (IV) and (V) was also previously reported. In the following paragraphs we describe in detail the methodologies for the synthesis of compound (VI) and its precursor with analytical data for these compounds.

EXAMPLE 1

Preparation of Methyl 2,3-di-O-benzyl-4-O-(4-nitrobenzoyl)-6-O-terbutyldimethylsilyl-α-D-glucopyranoside (VI)

Step 1: preparation of methyl 2,3-di-O-benzyl-6-O-terbutyldimethylsilyl-α-D-glucopyranoside.

A solution of (V) (4.4 g, 11.8 mmol), imidazole (4.02 g, 59 mmol) and TBDMSCl (3.03 g, 20.1 mmol) in 40 mL of dry DMF was vigorously stirred under argon at -40°C overnight. The solution was then diluted with 200 mL of CH_2Cl_2, washed with water, dried on sodium sulfate, filtered and concentrated. The product was purified by flash chromatography on silica gel (10% ethyl acetate/hexane) and the title compound was recovered as a colorless oil (5.5 g, 86% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)= 0.10 (s, 6H, $2CH_3$), 0.90 (s, 9H, 3 CH_3), 3.37 (s, 3H, CH_3O), 3.48 (dd, 1H, H2, $^3J_{2-3}$ = 9.7 Hz, $^3J_{1-2}$ = 3.4 Hz), 3.52-3.62 (m, 2H, H4 and H5), 3.80 (t, 1H, H3, $^3J_{2-3}$ = 9.7 Hz), 3.80 (d, 2H, H6, $^3J_{5-6}$ = 5.1 Hz), 4.61 (d, 1H, H1, $^3J_{1-2}$ = 3.4 Hz), 4.64 (d, 1H, H_{benz}, ^2J = 12.0 Hz), 4.75 (d, 1H, H_{benz}, ^2J = 12.0 Hz),

4.76 (d, 1H, H_{benz}, ^2J = 11.5 Hz), 4.97 (d, 1H, H_{benz}, ^2J = 11.5 Hz), 7.20-7.60 (m, 10H, H_{arom}). MS = 488.5 (M). $[\alpha]_D$ = +17.4°. Anal. calcd. for $C_{27}H_{40}O_6Si$ (448.7): C 66.36, H 8.25; found: C 67.10, H 8.76.

Step 2: preparation of compound (VI).

A solution of methyl 2,3-di-O-benzyl-6-O-terbutyldimethylsilyl-α-D-glucopyranoside (4.8 g, 9.8 mmol), pyridine (7.9 mL, 98.0 mmol) and PNBCl (3.6 g, 19.6 mmol) in 80 mL of dry dichloromethane was stirred under argon at room temperature overnight. The solution was then diluted with 100 mL of CH_2Cl_2, washed with water, dried on sodium sulfate, filtered and concentrated. The product was purified by flash chromatography on silica gel (10% ethyl acetate/hexane) and the title compound (VI) was recovered as a white solid (6.2 g, quantitative yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ(ppm) = -0.1 (s, 6H, $2CH_3$), 0.83 (s, 9H, 3 CH_3), 3.43 (s, 3H, CH_3O), 3.60-4.70 (m, 3H, H2 and 2H6), 3.84 (m, 1H, H5), 4.05 (t, 1H, H3, $^3J_{2-3}$ = $^3J_{3-4}$ = 9.6 Hz), 4.56 (d, 1H, H_{benz}, ^2J = 11.7 Hz), 4.66 (d, 1H, H1, $^3J_{1-2}$ = 4.0 Hz), 4.68 (d, 1H, H_{benz}, ^2J = 11.9 Hz), 4.79 (d, 1H, H_{benz}, ^2J = 11.9 Hz), 4.84 (d, 1H, H_{benz}, ^2J = 11.7 Hz (d, 1H, H1, $^3J_{1-2}$ = 3.4 Hz), 5.17 (t, 1H, H4, $^3J_{3-4}$ = $^3J_{4-5}$ = 9.9 Hz), 7.00-7.60 (m, 10H, H_{arom}), 8.00-8.30 (ΛΛ'BB' system, 4 H, $H_{4\text{-nitrobenzoyl}}$). MS = 637.4 (M). $[\alpha]_D$ = -23.1°. M.p. = 78.5 °C. Anal. calcd. for $C_{34}H_{43}NO_9Si$ (637.80): C 64.03, H 6.79, N 2.20; found: C 63.98,H 6.33, N 3.12.

EXAMPLE 2

Preparation of 3-C-[2,3-di-O-benzyl-4-O-(4-nitrobenzoyl)-α-D-glucopyranosyl]-1-propene (VII). The title compound can be prepared according to two alternative methods A and B, both described below.

Method A.

A solution of **(VI)** (5.75 g, 9.0 mmol), as per example 1, in 80 mL of H_2O/THF/AcOH (1:1:2) was vigorously stirred at room temperature for 2 hours. The mixture was then diluted with brine, neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (3×100 mL). The organic phase was dried on sodium sulfate, filtered and concentrated. The product was purified by flash chromatography on silica gel (40% ethyl acetate/hexane) and methyl 2,3-di-O-benzyl-4-O-(4-nitrobenzoyl)-α-D-glucopyranoside was recovered as a pale yellow solid (3.48 g, 73% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.42 (s, 3H, CH_3O), 3.60-3.70 (m, 2H, H2 and H6), 3.55 (dd, 1H, H6, $^2J_{6-6'}$ = 12.7 Hz, $^3J_{5-6}$ = 4.0 Hz), 3.80 (m, 1H, H5), 4.12 (t, 1H, H3, $^3J_{2-3} = {}^3J_{3-4}$ = 9.5 Hz), 4.63 (d, 1H, H_{benz}, ^2J = 11.9 Hz), 4.66 (d, 1H, H1, $^3J_{1-2}$ = 4.3 Hz), 4.68 (d, 1H, H_{benz}, ^2J = 11.7 Hz), 4.81 (d, 1H, H_{benz}, ^2J = 11.9 Hz), 4.88 (d, 1H, H_{benz}, ^2J = 11.7 Hz), 5.18 (t, 1H, H4, $^3J_{3-4} = {}^3J_{4-5}$ = 9.9 Hz), 7.00-7.60 (m, 10H, H_{arom}), 7.90-8.30 (AA'BB' system, 4 H, $H_{4\text{-nitrobenzoyl}}$). MS = 523.3 (M). $[\alpha]_D$ = -64.8°. M.p. = 125.1 °C. Anal. calcd. for $C_{28}H_{29}NO_9$ (523.56): C 64.23, H 5.58, N 26.75; found: C 65.11,H 6.34, N 26.73.

By working according to known methods (J.A. Bennek and G.R. Gray; J. Org. Chem. **1987**, 52, 892-897), a solution of methyl 2,3-di-O-benzyl-4-O-(4-nitrobenzoyl)-α-D-glucopyranoside (100 mg, 0.19 mmol) and BSTFA (36 μL, 0.14 mmol) in 0.5 ml of acetonitrile, was sealed and stirred for 1 h at 60 °C. Then the mixture was cooled at 0°C, allyltrimethylsilane (80 μL, 0.95 mmol) and TMSOTf (260 μL, 0.95 mmol) were added and the solution stirred at 0°C for 72 h. The solution was then diluted with 10 ml of ethyl acetate, washed with water, dried on sodium sulfate, filtered and concentrated. The product was purified by flash chromatography on silica gel (40% ethyl acetate/hexane) and the title compound (VII) was recovered as a colorless oil (40 mg, 40% yield on the alpha anomer, the beta anomer was present in a negligible quantity).

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm)= 2.51 (m, 2H, CH_2 allyl), 3.61 (m, 2H, H6), 3.70-3.80 (m, 1H, H5), 3.80 (dd, 1H, H2, $^3J_{1-2}$ = 5.1 Hz, $^3J_{2-3}$ = 8.4 Hz), 3.94 (t, 1H, H3, $^3J_{2-3} = {}^3J_{3-4}$ = 8.4 Hz), 4.15 (dt, 1H, H1), 4.66 (AB syst., 2H, H_{benz}), 4.74 (AB syst., 2H, H_{benz}), 5.12 (m, 1H, $H3'_{cis}$), 5.16 (t, 1H, H4, $^3J_{3-4} = {}^3J_{4-5}$ = 8.4 Hz), 5.21 (m, 1H, $H3'_{trans}$), 5.81 (m, 1H, H1'), 7.20-7.40 (m, 10H, H_{arom}), 8.30 (AA'BB' system, 4 H, $H_{4\text{-nitrobenzoyl}}$).

Method B.

Under inert argon atmosphere and dry conditions the compound of formula (VI) (1.4 g, 2.3 mmol) was dissolved in 5.75 mL of dry MeCN, allyltrimethylsilane (1.75 mL, 5 eq, 11 mmol) and trimethylsilyltriflate (1.99 mL, 5 eq, 11 mmol) were added and the mixture kept on stirring for 72 hours. The mixture was diluted with AcOEt and carefully kept at 0°C; then 22 mL of 1M aqueous NaOAc, previously stored in ice at 0°C were added. In this way, 22 mmol of base, exactly two times the eq. of TMSOTf were added, obtaining a buffer solution (pH 5). Mixing of the two phases, extraction with AcOEt,

washing to neutrality and evaporation afforded a crude mixture which by chromatography on silica gel (AcOEt-hexane 4:6) gave the pure product (VII) (880 mg; yield: 72%).

EXAMPLE 3

Preparation of 2,6:5,8-dianhydro-9-azido-4-O-benzyl-7,9-dideoxy-3-O-(4-nitrobenzoyl)-D-glycero-L-gulo-nonitol (IX).

Step 1: preparation of 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-iodo-3-O-(4-nitrobenzoyl)-D-glycero-L-gulo-nonitol (VIII).

To a solution of the C-glycoside (VII) (400 mg, 0.75 mmol) in dry THF (3 mL) cooled at 0°C in an ice-bath, I_2 (570 mg, 2.25 mmol) was added and the solution stirred at 0°C for 1 hr. The crude was then diluted with AcOEt (100 mL), 200 mL of water were added and the mixture was vigorously stirred at room temperature adding $Na_2S_2O_3$ portion-wise until the two phase discolored. The organic layer was washed with water, and the crude purified by flash chromatography (40% AcOEt/petroleum ether) affording the compound (VIII) as a yellow solid (260 mg, 61 % yield).

Step 2: preparation of compound (IX)

The n-Bu_4NN_3 was prepared from the commercial NaN_3 using the following procedure: 40% aqueous n-Bu_4NOH (23 ml) was diluted with water (23 ml) and a solution of NaN_3 (1140 mg, 35 mmol) in water (10 ml) was added and the solution was stirred 30 min at room temperature. The aqueous solution was extracted three times with $CHCl_3$ and the n-Bu_4NN_3 was recovered as a deliquescent colorless solid that solidified after removal of moisture by washing several times with toluene.

The iododerivative (VIII) (250 mg, 0.44 mmol) was dissolved in dry toluene (5 mL) under argon atmosphere, n-Bu_4NN_3 (375 mg, 1.32 mmol) was added and the solution was stirred at 60 °C 12 hrs. The reaction crude was concentrated in vacuo and purified by flash chromatography (50% AcOEt/petroleum ether) affording the title compound (IX) as a colorless solid (90 mg, 42% yield).

Compound (IX) is a mixture of diastereomers that are visible by TLC analysis (40% AcOEt/petroleum ether).

EXAMPLE 4

Preparation of 2,6-anhydro-4,5-di-O-benzyl-7,8,9-trideoxy-D-gluco-non-8-enitol (X) (also known as 6-allyl-4,5-bis-benzyloxy-2-hydroxymethyl-tetrahydropyran-3-ol).

Under inert atmosphere and dry conditions, methyl 2,3-di-O-benzyl-α-D-glucopyranoside (9.35 g, 23.95 mmol) was dissolved in 51.1 mL of dry MeCN. Allyl trimethylsilane (19.27 mL, 5 eq, 119 mmol) and trimethylsilyltriflate (21.63 mL, 4 eq, 97.3 mmol) were added and the mixture was stirred for 3 hours. The mixture was carefully kept at 0°C and diluted with AcOEt (150 mL) and water (150 mL), then Na_2CO_3 was added until neutrality. Mixing of the two phases, extraction with AcOEt and evaporation afforded a crude mixture which, by chromatography on silica gel (AcOEt-hexane 1:1), gave the title compound (X) (7.16 g; yield 78%).

$[M+H]+ = 385$; $[M+NH_4]+ = 402$.

^{1}H-NMR ($CDCl_3$), diagnostic signals δ (ppm): 7.4-7.2 (m, 10H), 5.8 (m, 1H), 4.0 (m, 1H), 2.5 (m, 2H).

EXAMPLE 5

Preparation of 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-iodo-D-glycero-L-gulo-nonitol (XI).

To a solution of 2,6-anhydro-4,5-di-O-benzyl-7,8,9-trideoxy-D-gluco-non-8-enitol (1 g, 2.6 mmol) in dry DCM (10.4 mL) cooled at 0°C in an ice-bath, I_2 (1.32 g, 2 eq., 5.2 mmol) was added and the solution stirred at 0 °C for 3 hr. The crude was then diluted with AcOEt (100 mL), 200 mL of water were added and the mixture was vigorously stirred at room temperature adding $Na_2S_2O_3$ portion-wise until the two phases discolored. The organic layer was washed with water, and the crude purified by flash chromatography (AcOEt-hexane 6:4) affording the title compound (XI), also known as 7-benzyloxy-5-hydroxymethyl-2-iodomethylhexahydrofuro[3,2-b]pyran-6-ol, as a yellow oil (800 mg, 74 % yield mixture of epimers).

$[M+H]+ = 421$; $[M+NH_4]+ = 438$.

^{1}H-NMR ($CDCl_3$), diagnostic signals δ(ppm): 7.4-7.2 (m, 5H), 4.6 (m, 1H), 3.3 (m, 2H), 2.2 (m, 1H) 2.0 (m, 1H).

EXAMPLE 6

Preparation of 2,6:5,8-dianhydro-9-azido-4-O-benzyl-7,9-dideoxy-D-glycero-L-gulo-nonitol (XII).

2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-iodo-D-glycero-L-gulo-nonitol (XI) (670 mg, 1.60 mmol) was dissolved in DMF (5 mL) under argon atmosphere, $Na^+N_3^-$ (207 mg, 2 eq., 3.19 mmol) was added and the solution was stirred at 50°C for 4 hrs. Then, the mixture was diluted with AcOEt (30 mL) and water (30 mL). Mixing of the two phases, extraction with AcOEt and evaporation afforded a crude mixture which, by chromatography on silica gel (AcOEt-hexane 6:4), gave the title compound (XII) as a colorless oil (593 mg, 100% yield).

[M-H]- = 334; [M+CH3COO]- = 395.

^{1}H-NMR ($CDCl_3$), diagnostic signals δ(ppm): 7.4-7.2 (m, 5H), 4.6 (m, 1H), 3.3 (m, 2H), 2.2 (m, 1H) 1.8 (m, 1H).

EXAMPLE 7

Oxidation of 2,3,4,6-tetra-O-benzyl-D-glucose

Method A (with Dess Martin Periodinane).

To a solution of the tetrabenzyl glucopyranoside (XIII) (1.5 g, 2.774 mmol, 1 eq.) in 27 mL of dry CH_2Cl_2, Dess Martin Periodinane (DMP) (1.76 g, 4.161 mmol, 1.5 eq.) was added. The resulting mixture was stirred at room temperature for 1 h, then 1 more eq. of DMP was added to push the reaction to completion. The reaction was diluted with Et_2O (50 mL) and treated with 50 mL of an aqueous solution containing 2.5 g of $NaHCO_3$ and 12.5 g of $Na_2S_2O_3$. The resulting mixture was then stirred until the organic phase became clear. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, H_2O, dried over sodium sulfate, filtered and volatiles were removed under reduced pressure. The crude tetra-O-benzylglucolactone was analysed by TLC and NMR and did not require further purification. Yield = 1.45 g (97%).

^{1}H NMR (200 MHz, $CDCl_3$): 3.7 (m, 2H, -C<u>H</u>$_2$O- H6); 3.96 (m, 2H, H3 + H4); 4.15 (d, 1H, H2 J= 5.5 Hz); 4.4-4.8 (m, 8H, H5 + 7 PhC<u>H</u>$_2$O-); 5.2 (d, 1H, PhHC<u>H</u>O- J= 11.4 Hz); 7.15-7.4 (m, 20H, <u>Ph</u>CH$_2$O-).

Method B (Swern oxidation).

Under argon atmosphere compound (XIII) (5g, 9.25 mmol, 0.04 M) was dissolved in 230 mL of the oxidant mixture DMSO/Ac_2O previously stirred for one hour with 4 A

molecular sieves. After 3 hours the reaction was completed (monitored by TLC: AcOEt-hexane 3:7). The reaction mixture was diluted with CH_2Cl_2 and H_2O-ice, the organic phase was carefully washed with H_2O in order to eliminate DMSO as much as possible. Excess of DMSO was evaporated under high vacuum. The crude was purified by flash chromatography on silica gel (AcOEt-hexane 1:9). 4.88 g of the tetra-O-benzylglucolactone were thus recovered as a pure product. Yield 98%.

EXAMPLE 8

Allylation of gluconolactone to get the compound of formula (XIV)

Under argon atmosphere the gluconolactone (5.138 g, 9.539 mmol, eq 1) was dissolved in 75 mL of dry Et_2O and cooled at -78°C in a mixture of acetone-CO_2. Allylmagnesium bromide (12.4 mL of a soln. 1 M in Et_2O, 12.4 mmol, 1.3 eq) was added drop-wise in 40 min. The reaction was stirred for 3 hours and checked by TLC (AcOEt-hexane 3:7). We transferred the reaction flask in an ice bath and the temperature was raised up to 0°C. 10 mL of a satured aqueous solution of $NH_4^+Cl^-$ were added drop-wise, to neutralize the unreacted Grignard reagent. The reaction mixture was diluted with AcOEt and the organic phase washed with 5% HCl aq. and then H_2O, dried and evaporated. The crude was purified by column chromatography on silica gel (AcOEt-hexane from 5:95 to 20:80). We recovered 4.4 g of the allylderivative 5,6,7,9-tetra-O-benzyl-1,2,3-trideoxy-D-gluco-non-1-en-4-ulopyranose (XIV) as a pure product. Yield 80%.

EXAMPLE 9

Stereoselective reduction with Et_3SiH, to get 2,6-anhydro-1,3,4,5-tetra-O-benzyl-7,8,9-trideoxy-L-glycero-L-gulo-non-8-enitol (XV).

Compound (XIV) (2.4 g, 4.133 mmol, eq 1) was dissolved under inert argon atmosphere in 25 mL of dry acetonitrile and cooled at −18° C (ice+salt bath). Et_3SiH (0.855 ml, 5.37 mmol, 1.3 eq.) and BF_3*Et_2O (0.52 mL, 4.133 mmol, 1 eq.) were added and the reaction was stirred for 1 hour. A TLC control revealed that the β-anomer completely reacted while the correspondent α-anomer did not react. After 90 minutes we added distilled water and solid $NaHCO_3$ to neutralize the acid, until the aqueous phase was basic. The organic phase was diluted with AcOEt and washed with water for 3 times, then dried and evaporated. The crude was purified by flash chromatography (AcOEt-hexane 1:9),

recovering 1.45 g of pure product (XV) (yield 63%), and 600 mg of unreacted α-anomer.

EXAMPLE 10

Preparation of the bicyclic azidoderivative 2,6:5,8-dianhydro-9-azido-1,3,4-tri-O-benzyl-7,9-dideoxy-L-glycero-L-gulo-nonitol (XVI).

Step 1: formation of the bicyclic iodoether derivative.

Under inert atmosphere compound (XV) (650 mg, 1.151 mmol, 1 eq.) was dissolved into 27 mL of dry CH_2Cl_2 and cooled at 0°C in an ice bath. I_2 (1.75 g, 6.09 mmol, 6 eq) was added (the final concentration of I_2 in the mixture had to be 0.25-0.30 M) and the reaction mixture was stirred at room temperature for six hours. The reaction was monitored with Maldi-TOF mass spectrometry following the complete disappearance of compound (XV). We added an aqueous solution of $Na_2S_2O_3$ shaking vigorously until the excess of iodine was destroyed (the brown colour disappeared) taking care to use the minimum quantity of reducing agent to prevent the demolition of the cycle. The organic phase was washed with water twice and then dried and evaporated. Flash chromatography with AcOEt-hexane from 1:9 to 4:6 was performed using the minimum amount of silica gel. We recovered 551 mg of the bicyclic iodomethylderivative as a pure product. Yield: 80%.

Step 2. Substitution with azide to get the compound (XVI).

The bicyclic iodomethylderivative (1.477 g, 2.46 mmol, 1 eq.) of step 1 was dissolved into 50 mL of dry toluene under inert atmosphere and then Bu_4NN_3 was added (3.5 g, 14.7 mmol, 5 eq). The reaction was stirred for 2 days at room temperature. The solvent was evaporated at 30°C with great care because Bu_4NN_3 might be explosive at higher temperatures, the crude was purified by flash chromatography (AcOEt-hexane 1 :9). We recovered 1.191 g of the bicyclic azidoderivative **(XVI)**. Yield: 94%.

NMR 1H, 300 MHz (mixture of diastereoisomers): δ (ppm): 2.05 (1H, m, H1'a), 2.3 (1H, q, H1'b), 3.18 (1H,q, H3'), 3.58 (7H, m, H1, H3, H4, H5, 2H6, H2'), 3.15 (1H, t, H2), 4.42-4.9 (6H, m, benzylic CH_2) , 7.28 (15H,m, H arom.)

EXAMPLE 11

Preparation of the bicyclic aminoderivative 9-amino-2,6:5,8-dianhydro-7,9-dideoxy-L-glycero-L-gulo-nonitol (II).

Method A. Catalytic hydrogenation of compound (XVI)

A solution of compound (XVI) (83 mg, 0.161 mmol, 1 eq.) in MeOH (3 mL) was treated with Pd/C (17 mg, 10 wt. %, 0.1 eq.) and acetic acid (0.1 mL, 1.75 mmol, 11 eq.). The reaction was stirred at room temperature under hydrogen atmosphere. TLC (AcOEt/hexane 4:6) showed the disappearance of the starting material and the reaction was continued until a single non-UV-visible spot was present (TLC: CH_2Cl_2/MeOH/TEA 7:3:1; R_f = 0.2). The reaction was filtered through a celite pad (2 cm thick), which was further washed several times with MeOH. Concentration of the combined filtrates under reduced pressure gave a colourless oil. Yield = 33 mg (73%) of (II) as acetic acid salt.

^{1}H NMR (200 MHz, CD_3OD): 2.0 (s, 3H, CH_3COO); 2.05-2.24 (m, 2H, H1'); 2.95-3.9 (m, 7H, H1 + H2 + H3 + H4 + H5 + H6 + H3'); 4.32 (m, 1H, H2').

Method B. Catalytic hydrogen transfer reduction of compound (XVI).

Compound (XVI) (262 mg, 0.508 mmol, 1 eq.) was dissolved into 10 mL of MeOH and $HCOONH_4$ (640 mg, 10.16 mmol, 20 eq) and 10% $Pd(OH)_2/C$ (26 mg) were added. The reaction was stirred at reflux temperature for 5 hours, TLC and Maldi-TOF mass controls revealed the disappearance of the starting material and the formation of other products of partial hydrogenation among which the principal was the target compound (II). TLC: AcOEt-hexane 4:6 for compound (XVI) and CH_2Cl_2-MeOH 7:3 for the final product (II). The catalyst was removed by filtration on celite and the solvent was then evaporated. After the addition of 5 mL of water, the aqueous phase was extracted 5 times with CH_2Cl_2. The organic phase was dried and evaporated to yield the crude (II), directly submitted to the following reaction for the amino group protection.

EXAMPLE 12

Allyloxycarbonylation of the amino group. Preparation of 9-{[(allyloxy)carbonyl]amino}-2,6:5,8-dianhydro-7,9-dideoxy-L-glycero-L-gulo-nonitol (XXIV).

A solution of the acetic acid salt of compound (II) (29 mg, 0.104 mmol, 1 eq.) in dioxane (0.5 mL) was treated with a 10% K_2CO_3 aqueous solution (1 mL) and cooled to 0°C. A solution of Alloc-Cl (22 µL, 0.208 mmol, 2 eq) in dioxane (0.5 mL) was added drop-wise and the reaction mixture was stirred for one hour at room temperature. When the ninhydrin test on TLC revealed the absence of unreacted NH_2 groups, reaction mixture was treated with acetic acid to pH=7 and volatiles were removed under reduced

pressure. Purification by flash-chromatography (DCM : MeOH 95/5) gave (XXIV) (24 mg, 76% yield).

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 2.0 (m, 2H, H1'); 3.1-3.9 (m, 9H, H1 + H2 + H3 + H4 + H5 + H6 + H3'); 4.44 (m, 1H, H2'); 4.55 (m, 2H, CH_2=CHC$\underline{H}_2$O-); 5.2 (m, 2H, C$\underline{H}_2$=CHCH$_2$O-); 5.67 (m, 1H, -CH$_2$OCON$\underline{H}$CH$_2$-); 5.92 (m, 1H, CH$_2$=C$\underline{H}$CH$_2$O-).

^{1}H NMR (200 MHz, CD_3OD): 2.05 (m, 2H, H1'); 3.1-3.9 (m, 9H, H1 + H2 + H3 + H4 + H5 + H6 + H3'); 4.3 (m, 1H, H2'); 4.57 (m, 2H, CH_2=CHC$\underline{H}_2$O-); 5.18-5.4 (m, 2H, C$\underline{H}_2$=CHCH$_2$O-); 5.98 (m, 1H, CH$_2$=C$\underline{H}$CH$_2$O-); 7.1 (m, 1H, -CH$_2$OCON$\underline{H}$CH$_2$- exchanges with deuterium within 20 minutes).

EXAMPLE 13

Preparation of the orthogonally protected derivative 9-{[(allyloxy)carbonyl] amino}-2,6:5,8-dianhydro-3-O-benzyl-1-O-[tert-butyl(dimethyl)silyl]-7,9-dideoxy-4-O-(4-nitrobenzoyl)-L-glycero-L-gulo-nonitol (XXV).

Step 1: Silylation of the primary hydroxy group.

A solution of (XXIV) (17.5 mg, 0.0577 mmol, 1eq.), imidazole (7.8 mg, 0.115 mmol, 2 eq.) and TBDMSCl (0.0635 mg, 9.6 mmol, 1.1 eq.) in 0.577 mL of dry DCM was vigorously stirred under nitrogen atmosphere at 0°C for 2 h. The solution was then diluted with 5 mL of water, and extracted several times with DCM (2 mL). The organic phase was dried over sodium sulfate, filtered and evaporated. The crude was analysed by TLC and NMR and did not require further purification. Yield = 23 mg (95%) of 6-O-silyl derivative.

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.1 (s, 6H, -Si(C$\underline{H}_3$)$_2$); 0.9 (s, 9H, -SiC(C$\underline{H}_3$)$_3$); 2.0 (m, 2H, H1'); 3.1-3.9 (m, 9H, H1 + H2 + H3 + H4 + H5 + H6 + H3'); 4.38 (m, 1H, H2'); 4.6 (m, 2H, CH_2=CHC$\underline{H}_2$O-); 5.3 (m, 2H, C$\underline{H}_2$=CHCH$_2$O-); 5.4 (m, 1H, -CH$_2$OCON$\underline{H}$CH$_2$-); 5.92 (m, 1H, CH$_2$=C$\underline{H}$CH$_2$O-).

Step 2: Mono-benzylation of secondary hydroxyl group at position 3.

Under an inert nitrogen atmosphere and dry conditions, the previous silyl derivative (23 mg, 0.055 mmol, 1 eq.) of step 1 and benzyl trichloroacetimidate (10 µL, 0.055 mmol, 1 eq) were dissolved in 275 µL of dry DCM and kept at 0°C. Trimethylsilyl trifluoromethanesulfonate (2 µL, 0.011 mmol, 0.2 eq) was added and the mixture was stirred for 2 hours at room temperature. The reaction mixture was then quenched with 2 µL of triethylamine and evaporated to give a crude product which was purified by flash

chromatography on silica gel (EtOAc-hexane 4:6) to give analytically pure 3-O-benzylated product (14.5 mg, 52 % yield).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.1 (s, 6H, -Si($C\underline{H}_3$)$_2$); 0.9 (s, 9H, -SiC($C\underline{H}_3$)$_3$); 2.0 (m, 2H, H1'); 3.2-3.5 (m, H, H1 + H4 + H5 + H3'); 3.57 (dd, 1H, H2 J_1= 9 Hz J_2 = 8.2 Hz); 3.65 (dd, 1H, H3 J_1= 8.7 Hz J_2= 8.6 Hz); 3.84 (dd, 1H, H6 J_{gem}= 10.7 Hz J_1= 4.6 Hz); 3.91 (dd, 1H, H6" J_{gem}= 10.7 Hz J_1= 4.93 Hz); 4.33 (m, 1H, H2'); 4.6 (m, 2H, CH_2=CHC$\underline{H}_2$O-); 4.75 (d, 1H, PhHC$\underline{H}$O- J_{gem}= 11.8 Hz); 4.93 (d, 1H, Ph$\underline{H}$CHO- J_{gem}= 11.8 Hz); 4.96 (bm, 1H, , -CH_2OCON$\underline{H}$CH_2-); 5.3 (m, 2H, C$\underline{H}_2$=CHCH_2O-); 5.95 (m, 1H, CH_2=C$\underline{H}$CH_2O-); 7.3-7.45 (m, 5H, $\underline{Ph}$-).

Step 3: p-nitrobenzoylation of the remaining secondary hydroxyl group in position 3 to get compound (XXV)

A solution of the previous 3-O-benzylated product (26 mg, 0.0512 mmol, 1 eq.) of step 2, pyridine (41 µL, 0.512 mmol, 10 eq.), PNBCl (19 mg, 0.102 mmol, 2 eq.) and DMAP (cat. amount) in 0.512 mL of dry dichloromethane was stirred, under nitrogen atmosphere, at room temperature overnight. The solution was then diluted with 2 mL of dichloromethane, washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The product was purified by flash chromatography on silica gel (EtOAc-hexane 2:8) to give analytically pure (XXV) (30 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): -0.1 (s, 6H, -Si($C\underline{H}_3$)$_2$); 0.83 (s, 9H, -SiC($C\underline{H}_3$)$_3$); 2.05 (m, 2H, H1'); 3.3 (m, 1H, H3'); 3.48-3.50 (m, 2H, H1 + H3'); 3.67-3.74 (m, 4H, H6 + H5 + H4); 3.78 (dd, 1H, H2 J_1= 8.88 Hz J_2= 8.89 Hz); 4.4 (m, 1H, H2'); 4.6 (d, 1H, PhHC$\underline{H}$O- J_{gem}= 12.5 Hz); 4.63 (m, 2H, CH_2=CHC$\underline{H}_2$O-); 4.82 (d, 1H, Ph$\underline{H}$CHO- J_{gem}= 12.5 Hz); 4.95 (bm, 1H, , -CH_2OCON$\underline{H}$CH_2-); 5.25-5.38 (m, 3H, C$\underline{H}_2$=CHCH_2O- + H3); 5.96 (m, 1H, CH_2=C$\underline{H}$CH_2O-); 7.15 (m, 5H, $\underline{Ph}$-); 8.1-8.3 (m, 4H, $NO_2\underline{Ph}$-).

EXAMPLE 14

De-silylation of compound (XXV) to get 9-{[(allyloxy)carbonyl]amino}-2,6:5,8-dianhydro-3-O-benzyl-7,9-dideoxy-4-O-(4-nitrobenzoyl)-L-glycero-L-gulo-nonitol (XXVI).

A solution of compound (XXV) (24 mg, 0.0366 mmol) in 1.2 mL of H_2O/THF/AcOH (1:1:2) was vigorously stirred at room temperature for 5 hours. The mixture was then diluted with brine, neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (3×2 mL). The organic phase was dried over sodium sulfate, filtered and evaporated in vacuo. The

product was purified by flash chromatography on silica gel (1:1 ethyl acetate/hexane) to give analytically pure compound (XXVI) (16 mg, 80% yield).

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 2.05 (m, 2H, H1'); 3.3-3.50 (m, 3H, H1 + H3'); 3.67-3.74 (m, 5H, H6 + H5 + H4 + H2); 4.4 (m, 1H, H2'); 4.6 (d, 1H, PhHC<u>H</u>O- J_{gem}= 12.2 Hz); 4.63 (m, 2H, CH_2=CHC<u>H</u>$_2$O-); 4.82 (d, 1H, Ph<u>H</u>CHO- J_{gem}= 12.2 Hz); 4.97 (bm, 1H, , -CH_2OCON<u>H</u>CH_2-); 5.2-5.40 (m, 3H, C<u>H</u>$_2$=CHCH$_2$O- + H3); 5.96 (m, 1H, CH_2=C<u>H</u>CH_2O-); 7.15 (m, 5H, <u>Ph</u>-); 8.1-8.3 (m, 4H, NO_2<u>Ph</u>-).

EXAMPLE 15

Loading of the C-glucoside (VII) onto a polymeric support [HMP (Wang) resin] through the primary hydroxyl group.

The HMP-trichloracetimidate resin (1g, maximum loading 0.8 mmol) was allowed to swell for 30 min in dry CH_2Cl_2 under argon atmosphere. Then the resin was washed well with dry THF to remove the moisture and suspended in 5 ml of anhydrous cyclohexane. A three-fold excess of C-glucoside (VII) (1280 mg, 2.4 mmol) dissolved in 2 mL of anhydrous CH_2Cl_2 and a catalytic amount of BF_3-OEt_2 (25 μL) were added to the suspension that was shaken for 10 min at room temperature under argon atmosphere. The resin was then washed with anhydrous CH_2Cl_2 and THF and the loading and washing cycle was repeated by recycling the C-glucoside (VII). The resin loaded with the C-allyl derivative (XVII) was finally dried overnight in vacuo. The loading was determined by cleaving a part of resin (100 mg) in TFA 10% in CH_2Cl_2 (2 ×30 min, room temperature) and resulted to be of 0.75 mmol/g (average value from three independent experiments of loading).

EXAMPLE 16

Selective deprotection of O-4 of the C-allylglucoside and ether formation on solid phase to get resin linked intermediate (XIX).

The resin linked intermediate (XVII) (linked through C6) was treated with a base in order to selectively deprotect the position 4 that was subsequently functionalized as n-butyl ether.

Step 1: resin linked intermediate (XVIII).

Method A. The resin (500 mg, about 0.4 mmol of bound sugar) was washed with anhydrous CH_2Cl_2 (10 mL×2) and THF (10 mL×2) under argon atmosphere, then was suspended in 10 mL of anhydrous DMF and a five-fold excess of KOtBu (220 mg, 2

mmol) was added. The solution turned to a dark blue color and the resin was stirred at room temperature for 2 hours under argon atmosphere. Three other cycles of hydrolysis of 2 hours each were performed to ensure a complete deprotection of the position 4. The solvent was finally removed and the resin washed with dry DMF, acetone, THF and DMF, affording the resin linked intermediate (XVIII).

Method B. 100 mg of resin (XVII) (0.45 mmol/g, $4.5*10^{-3}$ mmol) were washed 4 times with dry THF to remove moisture, suspended in dry THF (5 mL) under inert atmosphere and MeONa (0.5 M in MeOH, 7 eq., 0.312 mmol, 625 µL) was added. The suspension was shaken for 16 h at room temperature and drained. The resin was washed with DCM x2, DMF x2, MeOH x2, DMF x2 and DCM x3 and dried *in vacuo* overnight (absence of PNB ester was evaluated by TLC analysis after cleavage of 10 mg of resin) to give (XVIII).

Step 2: resin linked intermediate (XIX)

Method A. Resin -bound glycoside (XVIII) was O-alkylated in position 4 by the following way. To a suspension of the resin in 10 mL of anhydrous DMF, a five-fold excess of KOtBu (220 mg, 2 mmol) and of n-butyl bromide (215 µL, 2 mmol) and a catalytic amount of nBu_4NI (5 mg) were added and the mixture was shaken at room temperature overnight. The resin was then washed with anhydrous DMF, THF, CH_2Cl_2, DMF under argon atmosphere. The O-alkylation and washing cycle was repeated two other times. After the last cycle of reaction, the resin was washed with DMF, water, acetone, THF and dried in vacuo overnight affording the resin linked intermediate (XIX). 100 mg of dried resin were cleaved (10% TFA in CH_2Cl_2, 2× 30 min, room temperature) and the C-glucoside recovered in the effluents resulted to be almost pure according to TLC analysis. After purification by flash chromatography on silica gel (30% ethyl acetate/hexane), 26 mg of pure 3-C-[2,3-di-O-benzyl-4-O-(n-butyl)-α-D-glucopyranosyl]-1-propene were recovered, corresponding to a loading of 0.6 mmol/g.

^{1}H-NMR (200 MHz, $CDCl_3$): δ(ppm) = 0.90 (t, 3H, CH_3, J = 7.5 Hz), 1.30 (m, 2H, $C\underline{H}_2CH_3$), 1.50 (broad multiplet, 2H, $C\underline{H}_2CH_2CH_3$), 2.47 (m, 2H, H3'), 3.26 (t, 1H, H3 or H4), 3.40-3.80 (m, 7H, H2,H3 or H4, H5, H6, $-CH_2-O$), 4.02 (dt, 1H, H1), 4.64 (AB syst., 2H, CH_2Ph), 4.82 (AB syst., 2H, CH_2Ph), 5.10 (m, 2H, H1'), 5.80 (m, 1H, H2'), 7.2-7.4 (m, 10 H, H_{arom}). MS: m/z = 441 (M); 423 (M-18).

Method B. 40 mg of resin (XVIII) (0.48 mmol/g, $20*10^{-3}$ mmol) were washed 4 times with dry THF to remove moisture, suspended in dry DMF (2 mL) under inert atmosphere and KHMDS (5 eq., 0.100 mmol, 152 µL of 15 % solution in toluene) was added. The suspension was shaken for 15 min, then butyl bromide (22 µL, 10 eq., 0.200 mmol) and tetrabutyl ammonium iodide (1.5 mg, 0.2 eq., $4*10^{-3}$ mmol) were added and the resulting mixture was shaken for 2 h and drained. The conversion was followed by TLC after cleavage of a small aliquot of resin (10 mg). Other two cycles of reaction were performed. After the last cycle of reaction, the resin (XIX) was washed with DMF x2, MeOH x2 and DCM x3.

Method C. 40 mg of resin (XVIII) (0.48 mmol/g, $20*10^{-3}$ mmol) were washed 4 times with dry THF to remove moisture, suspended in dry DMF (2 mL) under inert atmosphere and KHMDS (5 eq., 0.100 mmol, 152 µL of 15 % solution in toluene) was added. The suspension was shaken for 15 min and the excess of base was removed by filtration under inert atmosphere. Butyl bromide (22 µL, 10 eq., 0.200 mmol) and tetrabutyl ammonium iodide (1.5 mg, 0.2 eq., $4*10^{-3}$ mmol) were added and the resulting mixture was shaken for 2 h and drained. The conversion was followed by TLC after cleavage of a small aliquot of resin (10 mg). Other two cycles of reaction were performed. After the last cycle of reaction, the resin (XIX) was washed with DMF x2, MeOH x2 and DCM x3.

EXAMPLE 17

Iodo-cyclization to bicyclic scaffold (XX) on solid phase. Preparation of 2,6:5,8-dianhydro-4-O-benzyl-3-O-butyl-7,9-dideoxy-9-iodo-D-glycero-L-gulo-nonitol (XXI).

Step 1: resin linked bicyclic compound (XX).

400 mg of the resin (XIX) (0.24 mmol of bound C-glucoside) were allowed to swell in dry CH_2Cl_2 for 30 min at room temperature under argon atmosphere, then were suspended in a solution of iodine (300 mg, 1.2 mmol) in 10 mL of anhydrous CH_2Cl_2 and shaken at room temperature for 24 h under argon atmosphere. The resin was then washed with anhydrous THF and CH_2Cl_2 and another cycle of reaction was performed. At the end of the reaction, the resin was carefully washed with THF, acetone and CH_2Cl_2 until the effluents were colorless and was dried in vacuo overnight to give the resin linked bicyclic compound (XX).

Step 2: preparation of the title compound (XXI)

A sample of 100 mg of dried resin (XX) was cleaved (10% TFA in CH_2Cl_2, 2×30 min) and compound (XXI) was recovered almost pure as judged from a preliminary TLC analysis. Iododerivative (XXI) revealed to be resistant to the acidic conditions of the cleavage and was purified by flash chromatography on silica gel (40% ethyl acetate/hexane). 96 mg of pure compound (XXI) were recovered corresponding to a loading of 0.5 mmol/g of the resin and to an almost quantitative yield of the iodocyclization step.

Iodoglycoside (XXI): ^{1}H-NMR (300 MHz, $CDCl_3$): δ(ppm) = 0.90 (t, 3H, CH_3, J = 7.5 Hz), 1.35 (m, 2H, $C\underline{H}_2CH_3$), 1.55 (m, 2H, $C\underline{H}_2CH_2CH_3$), 1.94 (dt, 1H, H3'A, $J_{3'A\text{-}3'B}$ = 13 Hz; $J_{3'\text{-}1}$ = $J_{3'\text{-}2'}$ = 6.0 Hz), 2.26 (dt, 1H, H3'B, $J_{3'A\text{-}3'B}$ = 13 Hz; $J_{3'\text{-}1}$ = $J_{3'\text{-}2'}$ = 6.8 Hz), 3.24 (m, 1H, H5), 3.26 (dd, 1H, H1'A), 3.32 (dd, 1H, H1'B), 3.30 (m, 1H, one of the two protons CH_2-O of n-butyl ether), 3.65 (m, 1H, H2'), 3.7-3.8 (m, 4H, H3, H6A, H6B and one of the two protons CH_2-O of n-butyl ether), 4.00 (t, 1H, H2, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 5.7Hz), 4.10 (bt, 1H, H4), 4.56 (dt, 1H, H1, $J_{1\text{-}2}$ = 5.7Hz; $J_{1\text{-}3'}$ = 6.0 Hz), 4.78 (AB syst., 2H, CH_2Ph), 7.2-7.4 (m, 5 H, H_{arom}). MS: m/z = 477 (M).

In the proton NMR spectrum of compound (XXI) two sets of signals are visible corresponding to two diastereomers (ratio between the isomers about 3:1) deriving from the formation of the asymmetric carbon C8 during the iodo-cyclization.

EXAMPLE 18

Loading of bicyclic azide (IX) onto Wang resin

Bicyclic azide (IX) (mixture of diastercoisomers) was loaded onto Wang resin activated as trichloroacetimidate by performing two cycles.

Wang trichloroacetimidate resin was prepared starting from commercially available Wang resin, according to known procedure (Hanessian S., Xie F. Tetrahedron Lett. **1998**, 39, 733-736).

Wang trichloroacetimidate resin (203 mg, 0.95 mmol/g, 0.193 mmol) was washed several times with dry THF to remove moisture, then a solution of (IX) (470 mg, 5 eq., 0.965 mmol) in dry DCM (3 ml) was added under inert atmosphere and the suspension shaken for 5 min at RT. BF_3•Et_2O (12 µL, 0.5 eq., 0.095 mmol) was added and the suspension was shaken for 15 min at RT. The resin was then washed with DCM (2 x 3 mL), THF (2 x 3 mL), MeOH (2 x 3 mL), DCM (4 x 3 mL) and dried in vacuo

overnight. The effluents were collected to recover the unloaded scaffold (IX), which was purified by filtration through a silica gel plug (eluant: n-hexane/ethyl acetate 6/4; weight of recovered (IX): 410 mg). To determine the loading, 49 mg of resin were cleaved with 20% TFA in CH_2Cl_2 (2 × 5 mL, 20 min) and pure azide (IX) was recovered after purification on a silica gel plug (10.5 mg indicating a loading of 0.44 mmol/g, corresponding to a 50% conversion).

The partially loaded resin (197 mg; 0.44 mmol/g of loaded scaffold; 0.44 mmol/g of free OH corresponding to 0.087 mmol of free OH) was washed, under inert atmosphere, several times with dry THF to remove moisture, then was suspended in dry DCM (2.9 ml) and trichloroacetonitrile (175 µL, 20.0 eq., 1.74 mmol) was added. A 1:9 DBU:DCM solution (110 µL corresponding to 11 µL, 0.85 eq., 0.074 mmol of pure DBU) was added drop-wise in 5 minutes to the suspension, then the resulting suspension was shaken for 40 minutes at room temperature, drained and washed with dry DCM twice. A second trichloroacetimidate formation cycle was performed with the same procedure, then the solution was drained and the resin washed with DMF (2 x 3 mL), DCM (2 x 3 ml), DMF (2 x 3 mL), DCM (4 x 3 mL) and dried in vacuo overnight. The Wang trichloroacetimidate resin so obtained was washed several times with dry THF under inert atmosphere to remove moisture, then a solution of (IX) (423 mg, 5 eq., 0.870 mmol) in dry CH_2Cl_2 (3 ml) was added and the suspension shaken 5 min at room temperature. $BF_3 \cdot Et_2O$ (11 µL, 0.5 eq., 0.087 mmol) was added and the suspension shaken for 15 min at room temperature. The resin was then washed with DCM (2 x 3 mL), THF (2 x 3 mL), MeOH (2 x 3 mL), DCM (4 x 3 mL) and dried in vacuo overnight to give a batch of the resin-linked derivative (XXII). The effluents were collected to recover the unloaded compound (IX), which was purified by filtration through a silica gel plug (eluant: n-hexane/ethyl acetate 6/4; weight of recovered (IX): 350 mg). To determine the loading, 68 mg the resin were cleaved with 20% TFA in CH_2Cl_2 (2 × 5 mL, 20 min) and pure azide (IX) was recovered after purification on a silica gel plug (20 mg indicating a loading of 0.60 mmol/g, corresponding to a 78% conversion).

EXAMPLE 19

Selective deprotection of the p-nitrobenzoyl ester (position 3). Preparation of resin-linked intermediate (b).

100 mg of resin (a) [also coded as (XXII)] (0.45 mmol/g, $4.5*10^{-3}$ mmol) were washed 4 times with dry THF to remove moisture, suspended in dry THF (5 mL) under inert atmosphere and MeONa (0.5 M in MeOH, 7 eq., 0.312 mmol, 625 µL) was added. The suspension was shaken for 16 h at room temperature and drained. The resin was washed with DCM x 2, DMF x 2, MeOH x 2, DMFx2 and DCM x 3 and dried *in vacuo* overnight to give (b) (absence of PNB ester was confirmed by TLC analysis after cleavage of 10 mg of resin). In order to verify the yield of loading and conversion the resin was cleaved with 20% TFA in CH_2Cl_2 (2 times × 1.0 mL, 20 min), and the related compound free-(b) was recovered after evaporation (18 mg). The crude compound was analyzed by TLC and ^1H NMR, and then purified by flash-chromatography. 10 mg were obtained.

^1H NMR (200 MHz, $CDCl_3$): 1.90 (m, 1H, HC<u>H</u> 1'); 2.20 (m, 1H, <u>H</u>CH 1'), 3.45 (m, 2H, H3'); 3.57-4.08 (m, 6H, H2, H3, H4, H5, H6); 4.15 (m, 1H, H2'); 4.56 (m, 1H, H1); 4.65 (d, 1H, -<u>H</u>CHPh, J = 12.6 Hz); 4.88 (d, 1H, -HC<u>H</u>Ph, J = 12.6 Hz); 7.3-7.55 (m, 5H, -Ph).

EXAMPLE 20

Regioselective solid phase attachment of a diol. Preparation of (XXIII).

Step 1: activation of the resin (PS-DES-SiCl).

100 mg of resin PS-DES-SiH (by Argonaut) (1.37 mmol/g, 0.138 mmol) were washed 4 times with dry THF to remove moisture, suspended in dry DCM (1.37 mL) under inert atmosphere and 1,3-dichloro-5,5-dimethylhydantoin (162 mg, 6 eq., 0.822 mmol) was added. The suspension was shaken for 1.5 h at room temperature and drained. The resin was washed with DCM x 2, DMF x 2, MeOH x 2, DMF x 2 and DCM x 3 and dried by nitrogen flux to get the resin PS-DES-SiCl. Absence of Si-H (stretching at 2094 cm^{-1}) was confirmed by IR analysis.

Step 2: loading of the substrate.

A solution of 2,6:5,8-dianhydro-9-azido-4-O-benzyl-7,9-dideoxy-D-glycero-L-gulo-nonitol (XII) (275.7 mg, 3 eq., 0.822 mmol) and imidazole (65.2 mg, 3.5 eq., 0.959 mmol) in dry DCM (4 mL) was added to the resin PS-DES-Si-Cl (theoretical 0.274 mmol) and shaken over night under inert atmosphere. The solution was filtered and the unloaded scaffold recovered. The resin was washed with DCM x 2, DMF x 2, MeOH x 2, DMF x 2 and DCM x 3 obtaining (XXIII), directly employed in the further reactions.

EXAMPLE 21

Functionalization of OH group at position 3. Ether formation to get compound (XXVII-C-k).

Method A.

100 mg of resin (XXIII) (1.3 mmol/g theoretical loading) were washed several times with dry THF to remove moisture, then suspended in dry THF (3 mL) under inert atmosphere. NaH (27.4 mg, 5 eq., 0.685 mmol) was then added and the suspension was shaken for 15 min. Then benzyl bromide (163 μL, 10 eq., 1.3 mmol) and tetrabutylammonium iodide (3.5 mg, 0.2 eq., 0.027 mmol) were added, and the resulting mixture was shaken overnight. Then the resin was washed with DMF x 2, MeOH x 2 and DCM x 3 and submitted to the further steps.

Successive steps comprised the azide reduction performed as described in method A of example 24, the reaction with isopropylisocyanate and successive cleavage from the resin performed analogously to what is described in example 30. Purification gave the N-isopropylureido derivative (XXVII-C-k).

Mass spectra: $[M+H]+ = 485$; $[M+CH_3COO]^- = 543$.

Method B.

180 mg of resin (b) (0.4 mmol/g) were washed several times with dry THF to remove moisture, then suspended in dry DMF (3 ml) under inert atmosphere. KHMDS (15% in toluene, 5 eq., 0.18 mmol, 120 μL) was added, and the suspension was shaken for 15 min. Then the alkylating agent (10 eq., 0.35 mmol) and tetrabutylammonium iodide (2.6 mg, 0.2 eq., 0.007 mmol) were added, and the resulting mixture was shaken overnight. A small amount of the resin was washed with DMF x 2, MeOH x 2 and DCM x 3 and absence/presence of starting material was evaluated by TLC analysis after cleavage.

EXAMPLE 22

Functionalization of OH group at position 3. Acylation. (Scheme 9)

We performed the esterification directly on resin (b) using 10 equivalents of 3-phenylpropionic acid (hydrocynnamic acid), 10 eq. of DIC and 10 eq. of DMAP as a base (see, for a general reference about the use of DIC/DMAP in esterification reactions on solid phase, Riguera et al. J. Org. Chem., **1999**, 64, 8063) in DCM, substantially as set forth in scheme (9). The completeness of the reaction was followed by cleavage of minute quantities of the resin (<10 mg) and TLC comparison with an original sample

synthesized in solution. Typically the reaction was completed after one overnight cycle with the quantities described above.

50 mg of resin (b) (0.43 mmol/g, $2.15*10^{-3}$ mmol) were suspended in dry DCM (2 mL) under inert atmosphere and 3-phenylpropionic acid (32 mg, 0.215 mmol, 10 eq.), DMAP (26 mg, 0.215 mmol, 10 eq.) and DIC (33 µL, 0.215 mmol, 10 eq.) were added. The suspension was shaken for 16 h at room temperature and drained. The resin was washed with DCM x 2, DMF x 2, MeOH x 2, DMF x 2 and DCM x 3 and dried in vacuo overnight (absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin) to give resin type (c). The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times × 0.5 mL, 20 min), and compound unloaded (c) (with R = phenylpropionyl) was recovered after evaporation (10 mg). The crude compound was analysed by TLC and ^1H NMR, and then purified by flash-chromatography (4 mg).

^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.90 (m, 1H, HCH 1'); 2.23 (m,1H, HCH 1'); 2.65 (m, 2H, $PhCH_2CH_2$-); 2.95 (m, 2H, $PhCH_2CH_2$-); 3.3-3.85 (m, 6H, H6+H5+H3+H3'); 3.90 (dd, 1H, H2 J_1= 4 Hz J_2= 4 Hz); 4.15 (m, 1H, H2'); 4.6 (m, 1H, H1); 4.70 (d, 1H, PhHCHO- J= 12.8 Hz); 4.8 (d, 1H, PhHCHO- J= 12.8 Hz); 4.97 (dd, 1H, H4 J_1= 6.8 Hz J_2= 6.8 Hz); 7.1-7.4 (m, 10H, Ph-).

Herewith below is reported a representative procedure for the acylation of the free OH at position 3.

500 mg of resin (b) (0.4 mmol/g, 0.2 mmol) were suspended in dry DCM (5 mL) under inert atmosphere and the carboxylic acid (2.00 mmol, 10 eq.), DMAP (245 mg, 2.00 mmol, 10 eq.) and DIC (313 µL, 2.00 mmol, 10 eq.) were added. The suspension was shaken for 16 h at room temperature and drained. The resin was washed with DCM x 2, DMF x 2, MeOH x 2, DMF x 2 and DCM x 3 and dried in vacuo overnight (absence of starting material was confirmed by TLC analysis after cleavage of 10 mg of resin).

EXAMPLE 23

Functionalization of OH group at position 3. Carbamoylation. (Scheme 10)

Step 1: preparation of resin (e)

100 mg of resin (b) (0.42 mmol/g, $4.2*10^{-2}$ mmol) were washed with dry THF (4 x 2 mL) under inert atmosphere. The resin was then suspended in 1.25 mL of THF and 4-nitrophenyl chloroformate (85 mg, 0.420 mmol, 10 eq.) and N-methyl morpholine (93 µL, 0.840 mmol, 20 eq.) were added. The suspension was shaken for 3 h at room

temperature and drained. A second cycle with the same quantities was performed for 3 h, then the solution was drained and the resin washed with THF (2 x 2 mL), DCM (2 x 2 mL) and THF (2 x 2 mL) obtaining resin (e).

Step 2:

The resin (e) was suspended in dry THF and butyl amine (125 µL, 1.26 mmol, 30 eq.) was added. The suspension was shaken overnight at room temperature, then the solution was drained and the resin was washed with DCM (2 x 2 mL), DMF (2 x 2 mL), DCM (2 x 2 mL), DMF (2 x 2 mL) and DCM (4 x 2 mL) and dried in vacuo overnight (absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin) to obtain a resin type (f).

The resin (f) was cleaved with 20% TFA in CH_2Cl_2 (2 timesx 2 ml, 20 min), and unloaded (f) (with R'' = butyl) was recovered after evaporation (22 mg). The crude compound was analyzed by TLC and ^{1}H-NMR, and then purified by flash-chromatography (8 mg).

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.92 (t, 3H, $C\underline{H}_3CH_2$ J= 7 Hz); 1.25-1.55 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2CH_2$); 1.92 (ddd, 1H, $\underline{H}CH$ 1' J_1= 3.7 Hz J_2= 6.5 Hz J_3= 11.5 Hz); 2.25 (m, 1H, HC$\underline{H}$ 1'); 3.18 (m, 2H, -$CH_2C\underline{H}_2OCO$-); 3.42 (m, 2H, H3'); 3.65-3.9 (m, 4H, H6+H5+H3); 3.97 (m, 1H, H2); 4.18 (m, 1H, H2'); 4.63 (m, 1H, H1); 4.7-4.9 (m, 4H, $PhC\underline{H}_2O$- + H4 + N$\underline{H}$); 7.34 (m, 5H, $\underline{Ar}$-).

EXAMPLE 24

Reduction of azido group on solid phase. Preparation of the resin-loaded aminoderivative (d).

Method A.

A clear solution of PPh_3 (210 mg, 0.8 mmol, 10 eq.), H_2O (144 µL, 8.0 mmol, 100 eq.) in THF (2880 µL) was added to 200 mg of resin (c) (0.4 mmol/g, 0.08 mmol) pre-swelled in DCM for 30 minutes. The resulting mixture was shaken overnight, the solution was removed and the resin was washed with THF x 2, DCM x 2, THF x 2 and DCM x 2. The TBNS test (visualizing the presence/absence of free amino groups was carried out as described in W.S. Hancock, J.E. Battersby, Anal. Biochem. **1976**, 71, 260-264) gave a favorable result: absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin. After the above mentioned washing cycles,

the resin (d) was kept under inert atmosphere and used immediately for the next reaction.

Method B

250 mg of resin (c) (0.4 mmol/g, 0.1 mmol) were suspended in THF (4 mL) and $SnCl_2$ (152 mg, 0.80 mmol, 8 eq.), thiophenol (327 µL, 3.2 mmol, 32 eq.), TEA (558 µL, 4 mmol, 40 eq.) were added to provide a solution that was 0.2 M, 0.8 M and 1.0 M in the reagents, respectively (see, for a general reference to $SnCl_2$/thiophenol reagent, K. Brakeman et al. Chem. Eur. J. **1999**, *5*, 2241-2252). The mixture was shaken for 3h. The resin was washed with DMF x 2, MeOH x 2, DMF x 2, MeOH x 2, DMF x 2 and DCM x 4. Both the colour tests (TBNS and dyed-pNO_2phenylglycolate test) gave positive results (absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin). After the above mentioned washing cycles, the resin (d) was kept under inert atmosphere and used immediately for the next reaction.

EXAMPLE 25

Functionalization of the free amino group at position 9. Solid phase synthesis of amide (l) having R = p.nitrophenyl and R' = phenyl. Compound 2,6:5,8-dianhydro-9-(benzoylamino)-4-O-benzyl-7,9-dideoxy-3-O-(4-nitrobenzoyl)-D-glycero-L-gulo-nonitol amide (XXVII-B-c).

Method A

Resin (d) (R = p.nitrophenyl) (50 mg, loading: 0.56 mmol/g, 0.028 mmol) was suspended in 2 mL of dry DMF, benzoic acid (7 mg, 2eq., 0.056 mmol), HBTU (21 mg, 2 eq., 0.056 mmol) and DIPEA (20 µL, 4 eq., 0.11 mmol) were added and the mixture was shaken at room temperature for 40 min. This coupling step was repeated twice. The resin was then washed with DMF (2×10 min) and CH_2Cl_2 (2×10 min) and dried in vacuum overnight obtaining resin (l) (R = p.nitrophenyl; R' = phenyl). The IR spectrum of the resin beads showed the appearance of the C=O stretching absorption band at 1680 cm^{-1}, typical of secondary amides in dilute solutions.

The amide was then cleaved treating the resin with 50% TFA in CH_2Cl_2 (2×30 min at room temperature) and 15 mg of pure amide 2,6:5,8-dianhydro-9-(benzoylamino)-4-O-benzyl-7,9-dideoxy-3-O-(4-nitrobenzoyl)-D-glycero-L-gulo-nonitol (XXVII -B-c) were recovered [corresponding to an almost quantitative conversion of the amine (d) into amide (l)]. The two diastereomeric forms of azide (c) (after cleavage from the resin) can

be separated, in the case of compound (XXVII-B-c), by using a mixture of AcOEt/petroleum ether (4:6) as eluant.

Method B

A solution of benzoic acid (34 mg, 4 eq, 0.2 mmol), DIC (43 μL, 4 eq , 0.2 mmol), and HOBt (38 mg, 4 eq, 0.2 mmol) in 2 mL of dry DMF was stirred at room temperature for 20 minutes. Resin (d) (R = p.nitrophenyl) (95 mg, loading 0.49mmol/g, 0.046 mmol) was suspended in 1 mL of dry DMF with DIPEA (96 μL, 8 eq, 0.4 mmol), and then the solution of the pre-activated carboxylic acid was added in the reactor. The suspension was shaken at room temperature for 45 minutes and then the reaction mixture was filtered, washed with DMF x 2, DCM x 2, Et_2O and dried in vacuum for 1 hour, obtaining resin (l) (R = p.nitrophenyl; R' = phenyl).

The resin was cleaved with TFA 20% in DCM (2x20 min) and washed with THF x 2 and DCM x 2. After evaporation of the solvent, 18 mg of crude benzamide were obtained.

The mixture was then purified by chromatography on silica gel (AcOEt/ hexane 9:1) recovering mg 4 of pure benzamide (XXVII-B-c).

Method C

A more drastic acylation method, by using HATU [O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate] as strong condensating agent was also set up. Resin (d) (R = p.nitrophenyl) (mg 150, loading 0.38 mmol/g, 0.057 mmol) was suspended in 4 mL of dry DMF/DCM 1:1 and HATU (mg 87, 4 eq, 0.228 mmol), DIPEA (78 μL, 8 eq, 0.456 mmol) and benzoic acid (28 mg, 4 eq, 0.228 mmol) were added. The reaction was shaken for 45 minutes, then filtered and washed with DMF x 2, DCM x 2, THF. The coupling reaction was repeated 4 times and after every coupling cycle the presence of unreacted free amino groups was revealed with dyed-pNO_2phenylglycolate test. According to this method, the amine was revealed by a colourimetric assay directly on few beads suspended in 100 μL of a 0.002 M solution of the reagent (NF31) in MeCN (see De Clercq et al. Eur. J. Org. Chem. 1999, 2787).

After heating at 70°C for 10 minutes in a sand-bath, the beads were rapidly washed with DMF, MeOH and DCM (3 times for each solvent), obtaining resin (l) (R = p.nitrophenyl; R' = phenyl).

The resin was then cleaved with TFA 20% in DCM (2 x 20 min) and washed with THF and DCM. We recovered 25 mg of crude and, after chromathography, 11 mg of pure (XXVII-B-c). Yield: 34 %.

^{1}H NMR (300 MHz, $CDCl_3$) mixture of diastereoisomers, δ (ppm): 2.06 (m, 1H, H1'a), 2.42 (m, 1H, H1'b), 3.61 (m, 1H, H3'a), 3.71 (m, 1H, H3'b), 3.68-4.18 (m, 4H), 4.40 (bd, 1H, H2'), 4.61 (bs, 1H, H1), 4.73 (bs, 2H, $PhCH_2$), 5.15 (bs, 1H, H4), 7.08 (s, 1H, NH amide), 7.32 (m, 8H, PhH), 7.61 (AB system, 2H, H benzoic), 8.02 (AB system, 4H, H PNB-ester).

EXAMPLE 26

Preparation of caprylylamide. 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-3-O-(4-nitrobenzoyl)-9-(octanoylamino)-D-glycero-L-gulo-nonitol (XXVII-B-d).

Method A. A solution of caprylic acid (44 μL, 4 eq, 0.2 mmol), DIC (43 μL, 4 eq, 0.2 mmol) and HOBt (38 mg, 4 eq, 0.2 mmol) in dry DMF was stirred for 20 minutes and added to the suspension of resin (d) (R = p.nitrophenyl) (100 mg, loading 0.49 mmol/g, 0.049mmol), DIPEA (96 μL, 8 eq, 0.4 mmol) in 1 mL of dry DMF. The suspension was shaken for 45 minutes, then filtered and washed with DMF x 2, DCM x 2, Et_2O and dried in vacuo for 1 hr to get resin (l) (R = p.nitrophenyl; R' = n.heptyl), stored overnight at -18°C.

The resin was and then cleaved with TFA 20% in DCM (2 x 20 min) and washed with THF x 2 and DCM x 2. The cleavage afforded 34 mg of crude product that, after silica gel chromatography (AcOEt-hexane 9:1), gave 4 mg of pure amide (XXVII-B-d) with 15 % yield.

Method B

Resin (d) (R = p.nitrophenyl) (mg 150, loading 0.38 mmol/g, 0.057 mmol) was suspended in 4 mL of a mixture of DMF/DCM dry 1:2 and HATU (mg 87 , 4 eq, 0.228 mmol), DIPEA (78 μL, 8 eq, 0.456 mmol) and caprylic acid (36 μL, 4 eq, 0.228 mmol) were added. The reaction was shaken for 45 minutes and then filtered and washed exactly as in method C of example 25. In the same way and by using dyed-pNO_2phenylglycolate test, we still found the presence of unreacted amino groups after the fourth coupling cycle, and we thus proceeded with the fifth one until the test was negative, to obtain resin (l) (R = p.nitrophenyl; R' = n.heptyl).

The resin was cleaved with TFA 20% in DCM (2x20 min) and washed with THF and DCM. We recovered 28 mg of crude and, after chromatography, 9 mg of pure amide (XXVII-B-d). Yield: 27 %.

^{1}H NMR (200 MHz, $CDCl_3$) mixture of diastereoisomers, δ (ppm): 0.89 (m,3H,-CH_3), 1.40-1.95 (m, 10H, H), 2.05 (m, 2H,CH_2-CO), 2.14 (m,1H,H1'a), 2.33 (m,1H,H1'b), 3.53 (m,2H, H3'), 3.68-4.39 (m, 5H), 4.61 (m, 1H, H1), 4.75 (bs,2H, CH_2-Ph), 5.25 (q,1H, H4), 5.19 and 6.08 (m,1H, NH of the two diast.), 7.49 and 7.68 (m, 5H), 8.22 (AB system, 4 H).

EXAMPLE 27

Representative procedure for the acylation of the free NH_2 at position 9 with other carboxylic acids. Preparation of 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-3-O-(1-naphthylacetyl)-9-[(3-phenylpropanoyl)amino]-D-glycero-L-gulo-nonitol (XXVII-B-a) and of 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-[(3,5-dimethoxybenzoyl)-amino]-3-O-(1-naphthylacetyl)-D-glycero-L-gulo-nonitol (XXVII-B-b).

This procedure is essentially similar to the described in method C of example 25, but may use fewer cycles with longer reaction times.

A 4 mL DMF/DCM (1:1 ratio) solution of acid R'COOH (e.g. R' = 3,5-$(OMe)_2C_6H_3$-, or R' = $PhCH_2CH_2$-) (0.500 mmol, 5 eq.), HATU (190 mg, 0.500 mmol, 5 eq.) and DIPEA (171 µL, 1.00 mmol, 10 eq.) was added to resin (d) (e.g. with R = 1-naphtyl-CH_2-) (250 mg, 0.4 mmol/g, 0.1 mmol, 1 eq.). Subsequently, the resulting slurry was shaken for 3 days, the solution was drained, and the resin was washed with DCM x 2, DMF x 2 and DCM x 3. The dyed-pNO_2phenylglycolate test gave a pale red staining (about 2-5% free amines). A second cycle with the same quantities was performed for 48 hours, then the solution was drained and the resin washed with DCM x 2, DMF x 2, DCM x 2, DMF x 2 and DCM x 3 and dried in vacuo overnight (TNBS test and the dyed-pNO_2phenylglycolate test were negative after the second cycle) to obtain a resin type (g). The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times × 2.5 mL, 20 min), and crude compounds (XXVII-B-a) (52 mg) and (XXVII-B-b) (44 mg) were recovered after evaporation. They were analyzed by TLC and ^{1}H NMR, and then purified by flash-chromatography, thus yielding 21 mg of (XXVII-B-a) and 14 mg of (XXVII-B-b).

(XXVII-B-a) - ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.67 (m, 1H, HCH 1'); 2.16 (m, 1H, HCH 1'); 2.36 (m, 2H, $PhCH_2CH_2$-); 2.92 (m, 2H, $PhCH_2CH_2$-); 3.35 (m, 2H, H3');

3.55-3.8 (m, 5H, H6+H5+H3+H2); 4.05 (m, 3H, H2'+ ArC$\underline{H}_2$COO-); 4.45 (m, 1H, H1); 4.56 (m, 2H, PhC$\underline{H}_2$O-); 4.96 (dd, 1H, H4 J_1= 5.1 Hz J_2= 5.2 Hz); 5.95 (m, 1H, -CON$\underline{H}$-); 7.1-7.5 and 7.7-7.95 (m, 17H, $\underline{Ar}$-).

(XXVII-B-b) - ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 2.03 (m, 1H, $\underline{H}$CH 1'); 2.35 (m, 1H, HC$\underline{H}$ 1'); 3.37 (m, 2H, H3'); 3.58-3.88 (m, 11H, H6+H5+H3+H2+C$\underline{H}_3$OAr); 4.05 (m, 2H, ArC$\underline{H}_2$COO-); 4.28 (m, 1H, H2'); 4.55 (m, 1H, H1); 4.61 (d, 2H, PhC$\underline{H}_2$O- J= 2.75 Hz); 5.0 (m, 1H, H4); 5.9 (m, 1H, -CON$\underline{H}$-); 7.1-7.5 and 7.7-7.95 (m, 17H, $\underline{Ar}$-).

EXAMPLE 28

Azide reduction of the carbamoylderivative and acylation of the amino group on solid phase. Preparation of 2,6:5,8-dianhydro-4-O-benzyl-3-O-[(butylamino)carbonyl]-7,9-dideoxy-9-[(3-phenylpropanoyl)amino]-D-glycero-L-gulo-nonitol (XXVII-B-c).

Following method B of example 24, the carbamoylderivative resin-linked type (f) (e.g. with R'' = n.butyl) was functionalized also in the 3' position through ($SnCl_2$/PhSH/TEA) reduction of the azide to amine. The resulting free amino group was acylated (e.g. with phenylpropionic acid) by working according to the procedure of example 27, to give the resin type (h) (with R'' = n.butyl, R' = 2-phenylethyl).

The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times× 2 mL, 20 min), and compound (XXVII-B-e) was recovered after evaporation (50 mg). The crude compound was analyzed by TLC and ^{1}H NMR, and purified by flash-chromatography. 25 mg of pure (XXVII-B-e) were obtained; yield for the five steps: 55%.

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.92 (t, 3H, C$\underline{H}_3$CH$_2$ J= 7 Hz); 1.25-1.55 (m, 4H, CH$_3$C$\underline{H}_2$C$\underline{H}_2$CH$_2$); 1.75 (ddd, 1H, $\underline{H}$CH 1' J_1= 2.5 Hz J_2= 5.7 Hz J_3= 8.26 Hz); 2.25 (m, 1H, HC$\underline{H}$ 1'); 2.5 (m, 2H, PhCH$_2$C$\underline{H}_2$CO-); 2.95 (m, 2H, PhC$\underline{H}_2$CH$_2$CO-); 3.18 (m, 2H, -CH$_2$C$\underline{H}_2$OCO-); 3.44 (m, 2H, H3'); 3.65-3.86 (m, 4H, H6+H5+H3); 3.97 (m, 1H, H2); 4.13 (m, 1H, H2'); 4.51 (m, 1H, H1); 4.72 (s, 2H, PhC$\underline{H}_2$O-); 4.84 (dd, 1H, H4 J_1= 5 Hz J_2= 5.5 Hz); 4.92 (bt, 1H, -CH$_2$N$\underline{H}$COO- J= 5.6 Hz); 6.14 (m, 1H, -CH$_2$N$\underline{H}$COCH$_2$-); 7.15-7.4 (m, 10H, $\underline{Ar}$-).

EXAMPLE 29

Representative procedure for the sulfonylation of the free NH_2 at position 9. Preparation of 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-{[(4-methylphenyl)-sulfonyl]amino}-3-O-(3-phenylpropanoyl)-D-glycero-L-gulo-nonitol (XXVII-B-g).

200 mg of resin (d) (R = 2-phenylethyl) (0.4 mmol/g, 0.080 mmol) were suspended under inert atmosphere in dry DCM (2 mL) and DMAP (196 mg, 1.60 mmol, 20 eq.), tosyl chloride (153 mg, 0.80 mmol, 10 eq.) were added. After the resulting mixture was shaken for 5h, the solution was removed and the resin was washed with DCM x 2, DMF x 2 and DCM x 3. After the first cycle, the TNBS test gave a pale red staining. A second cycle was performed overnight, then the resin was washed with DCM x 2, DMF x 2 DCM x 2, DMF x 2 and DCM x 3 and dried in vacuo overnight (TNBS test was negative after the second cycle) giving a resin type (m).

The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times× 2.0 ml, 20 min), and compound (XXVII-B-g) was recovered after evaporation (40 mg). The crude compound was analyzed by TLC and ^1H NMR, and then purified by flash-chromatography. 6 mg of pure (XXVII-B-g) were thus obtained.

^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.7 (m, 1H, HCH 1'); 2.17 (m, 1H, HCH 1'); 2.4 (s, 3H, CH_3PhSO_2NH-); 2.68 (m, 2H, $PhCH_2CH_2$-); 2.95 (m, 2H, $PhCH_2CH_2$-); 3.25 (m, 2H, H3'); 3.55-3.7 (m, 5H, H6+H5+H3+H2); 4.05 (m, 1H, H2'); 4.5 (m, 1H, H1); 4.68 (m, 2H, $PhCH_2O$-); 4.95 (dd, 1H, H4 J_1= 5.5 Hz J_2= 5.4 Hz); 5.07 (m, 1H, -SO_2NH-); 7.15-7.38 (m, 12H, Ar-); 7.7 (d, 2H, *o*-SO_2Ar J= 9.2 Hz).

EXAMPLE 30

Representative procedure for the formation of ureido moiety at position 9. Preparation of 2,6:5,8-dianhydro-9-[(anilinocarbonyl)amino]-4-O-benzyl-7,9-dideoxy-3-O-(3-phenylpropanoyl)-D-glycero-L-gulo-nonitol (XXVII-C-a) and of 2,6:5,8-dianhydro-9-[(anilinocarbonyl)amino]-4-O-benzyl-7,9-dideoxy-3-O-octanoyl-D-glycero-L-gulo-nonitol (XXVII-C-b).

200 mg of resin (d) (R = 2-phenylethyl or R = n.heptyl) (0.40 mmol/g, 0.080 mmol) were suspended under inert atmosphere in dry DCM (2 mL) and TEA (11 µL, 0.080 mmol, 1 eq.) and phenyl isocyanate (87 µL, 0.80 mmol, 10 eq.) were added. After the resulting mixture was shaken for 5h, the solution was removed by suction and the resin was washed with DCM x 2, DMF x 2 and DCM x 3. After the first cycle the TNBS test was negative, while the dyed-pNO_2phenylglycolate test, mentioned in the text, gave a pale red staining. A second cycle with the same quantities was performed overnight and the resin was washed with DCM x 2, DMF x 2 DCM x 2, DMF x 2 and DCM x 3 and dried in vacuo overnight.) to get a resin type (n).

The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times× 2.0 mL, 20 min), and compounds (XXVII-C-a) (40 mg) and (XXVII-C-b) (32 mg) were recovered after evaporation. The crude compounds were analyzed by TLC and ^1H NMR, and then purified by flash-chromatography obtaining 10 mg of (XXVII-C-a) and 16 mg of (XXVII-C-b).

(XXVII-C-a) - ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.85 (m, 1H, HCH 1'); 2.24 (m, 1H, HCH 1'); 2.60 (m, 2H, $PhCH_2CH_2$-); 2.91 (m, 2H, $PhCH_2CH_2$-); 3.37-3.65 (m, 5H, H6+H5+H3'); 3.72 (m, 1H, H3); 3.85 (t, 1H, H2 J= 4 Hz); 4.12 (m, 1H, H2'); 4.54 (m, 1H, H1); 4.68 (m, 2H, $PhCH_2O$-); 4.91 (dd, 1H, H4 J_1= 6 Hz J_2= 5.9 Hz); 5.35 (bt, 1H, -CH_2NHCO-); 6.68 (s, 1H, -CONHPh); 7.1-7.4 (m, 15H, Ph-). Mass spectrum m/z (FAB$^+$) 561 (M^++1).

(XXVII-C-b) - ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.85 (pt, 3H, CH_3- J_1= 6.7 Hz J_2=6 Hz); 1.27 (bs, 8H, $CH_3CH_2CH_2CH_2CH_2$-); 1.6 (m, 2H, - CH_2CH_2CO-); 1.90 (m,1H, HCH 1'); 2.2-2.4 (m, 3H, HCH 1' + - CH_2CH_2CO-); 3.48 (m, 2H, H3'); 3.6-3.81 (m, 4H, H6 + H5 +H3); 3.86 (m, 1H, H2); 4.16 (m, 1H, H2'); 4.54 (m, 1H, H1); 4.7 (s, 2H, $PhCH_2O$-); 4.92 (t, 1H, H4 J= 5.9 Hz); 5.38 (bt, 1H, -CH_2NHCO-); 6.69 (s, 1H, -CONHPh); 7.25-7.4 (m, 10H, Ph-).

By working in an analogous way and by starting from 100 mg of resin (d) (R = p.nitrophenyl), the recovered crude product (25 mg) was chromatographed on silica gel (AcOEt/hexane 9:1) affording 4 mg (yield= 15%) of the pure ureidoderivative, 2,6:5,8-dianhydro-9-[(anilinocarbonyl)amino]-4-O-benzyl-7,9-dideoxy-3-O-(4-nitrobenzoyl)-D-glycero-L-gulo-nonitol **(XXVII-C-c)**.

^1H NMR (200 MHz, $CDCl_3$) mixture of diastereoisomers, δ (ppm): 2.30 (m, 2H, H-1'), 3.21-4.30 (m, 8H), 4.61 (m, 1H, H-1), 4.71 (bs, 2H, CH_2Ph), 5.19 (m, 1H, H-4), 6.35 (1H, NH), 6.75 (1H, NH), 7.3 (m, 10H, PhH), 8,2 (m, 4H, pNO_2PhH).

EXAMPLE 31

Representative procedure for thiourea formation at position 9. Preparation of 2,6:5,8-dianhydro-9-[(anilinocarbonothioyl)amino]-4-O-benzyl-7,9-dideoxy-3-O-(3-phenylpropanoyl)-D-glycero-L-gulo-nonitol (XXVII-C-d)

120 mg of resin (d) (R = 2-phenylethyl) (0.28 mmol/g, 0.034 mmol) were suspended under inert atmosphere in dry DCM (2 mL), TEA (5 µL, 0.034 mmol, 1 eq.) and phenyl isothiocyanate (41 µL, 0.340 mmol, 10 eq.) were added. The resulting mixture was then

shaken overnight; the solution removed by suction and the resin washed with DCM (2 x 2 mL), DMF (2 x 2 mL), DCM (2 x 2 mL), DMF (2 x 2 mL) and DCM (4 x 2 mL). After the first cycle the TNBS test was negative, while the dyed-pNO_2phenylglycolate test gave a pale red staining. A second cycle with the same quantities was performed overnight and the resin was washed with with DCM (2 x 2 mL), DMF (2 x 2 mL), DCM (2 x 2 mL), DMF (2 x 2 mL) and DCM (4 x 2 mL) obtaining a resin type (o).

The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times × 2.0 mL, 20 min), and compound (XXVII-C-d) was recovered after evaporation (13 mg). The crude compound was analyzed by TLC and ^{1}H NMR, and then purified by flash-chromatography. 5 mg of pure compound (XXVII-C-d) were obtained; yield for the four steps: 21%.

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.84 (m, 1H, HCH 1'); 2.3 (m, 1H, HCH 1'); 2.55 (m, 2H, $PhCH_2CH_2$-); 2.92 (m, 2H, $PhCH_2CH_2$-); 3.4-3.9 (m, 6H, H6+H5+H3+H3'); 3.96 (m, 1H, H2); 4.25 (m, 1H, H2'); 4.47 (m, 1H, H1); 4.54 (d, 1H, PhHCHO- J= 11.9 Hz); 4.64 (d, 1H, PhHCHO- J= 11.9 Hz); 4.82 (dd, 1H, H4 J_1= 6.3 Hz J_2= 6.2 Hz); 6.8 (bt, 1H, -CH_2NHCS-); 7.12-7.38 (m, 15H, Ar-); 7.6 (s, 1H, -CSNHPh).

EXAMPLE 32

Representative procedure for the reductive alkylation of the free amino group at position 9.

200 mg of resin (d) (R = 2-phenylethyl) (0.42 mmol/g, 0.084 mmol) were suspended under inert atmosphere in trimethyl orthoformate (TMOF) (2.5 mL) and the aldehyde (benzaldehyde or p.methoxybenzaldehyde) (1.68 mmol, 20 eq.) was added. After the resulting mixture was shaken overnight at room temperature, the solution was removed by suction and the resin was washed with TMOF (2 x 4 mL). After the first cycle the TNBS test was positive. Therefore a second cycle with the same quantities was performed for 3 h and the resin was washed with TMOF (2 x 4 mL). The resin was suspended in TMOF (2.5 mL) and AcOH (25 µL, 1% in TMOF) and $NaCNBH_3$ (106 mg, 1.68 mmol, 20 eq.) were added. The suspension was shaken for 3 h at room temperature, then the solution was drained and the resin was washed with DMF (2 x 3 mL), MeOH (2 x 3 mL), 10%TEA/DCM (1 x 4 mL), MeOH (2 x 3 mL), DCM (2 x 3 mL), MeOH (2 x 3 mL) and DCM (2 x 3 mL). After the above mentioned washing cycles, the resin type (p) (R = 2-phenylethyl, R' = phenyl or p.methoxyphenyl) was kept

under inert atmosphere and used immediately for the functionalization of the secondary amine.

EXAMPLE 33

Procedure for the urea formation of the secondary amino group at position 9. Preparation of 2,6:5,8-dianhydro-9-[(anilinocarbonyl)(benzyl)amino]-4-O-benzyl-7,9-dideoxy-3-O-(3-phenylpropanoyl)-D-glycero-L-gulo-nonitol (XXVII-C-e).

120 mg of resin (p) (R = 2-phenylethyl, R' = phenyl) (0.28 mmol/g, 0.034 mmol) were suspended under inert atmosphere in dry DCM (2 mL) and TEA (5 μL, 0.034 mmol, 1 eq.) and phenyl isocyanate (37 μL, 0.34 mmol, 10 eq.) were added. After the resulting mixture was shaken overnight, the solution was removed by suction and the resin was washed with DCM x 2, DMF x 2 and DCM x 3. After the first cycle the dyed-pNO_2phenylglycolate test gave a pale red staining. A second cycle with the same quantities was performed overnight and the resin was washed with DCM (2 x 2 mL), DMF (2 x 2 mL) DCM (2 x 2 mL), DMF (2 x 2 mL) and DCM (3 x 2 mL) and dried in vacuo overnight, to obtain a resin type (r).

The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times × 2.0 mL, 20 min), filtering and solvent evaporation afforded 30 mg of crude product. The crude compound was analyzed by TLC and ^1H NMR, and then purified by flash-chromatography.

7 mg of pure (XXVII-C-e) were obtained; yield for the six steps: 38%.

^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.85 (m, 1H, HCH 1'); 2.27 (m, 1H, HCH 1'); 2.45 (m, 2H, $PhCH_2CH_2$-); 2.82 (m, 2H, $PhCH_2CH_2$-); 3.48-3.74 (m, 5H, H6+H5+H3'); 3.87 (m, 1H, H3); 3.92 (m, 1H, H2); 4.06 (m, 1H, H2'); 4.57-4.75 (m, 5H, H1+$PhCH_2O$+ $PhCH_2N$); 5.0 (dd, 1H, H4 J_1= 6 Hz J_2= 5.9 Hz); 6.95-7.4 (m, 20H, Ar-); 7.7 (s, 1H, -CONHPh).

EXAMPLE 34

Procedure for the acylation of the secondary amino group at position 9. Preparation of 2,6:5,8-dianhydro-4-O-benzyl-9-[benzyl(octanoyl)amino]-7,9-dideoxy-3-O-(3-phenylpropanoyl)-D-glycero-L-gulo-nonitol (XXVII-B-f) and of 2,6:5,8-dianhydro-4-O-benzyl-9-[benzyl(1-naphthylacetyl)amino]-7,9-dideoxy-3-O-(3-phenylpropanoyl)-D-glycero-L-gulo-nonitol (XXVII-B-h).

A 3 mL DMF/DCM (1:1 ratio) solution of carboxylic acid (e.g. caprylic acid or napht-1-ylacetic acid) (0.270 mmol, 5 eq.), HATU (103 mg, 0.270 mmol, 5 eq.) and DIPEA (93 μL, 0.540 mmol, 10 eq.) was added to resin (p)) (R = 2-phenylethyl, R' = phenyl or p.methoxyphenyl) (194 mg, 0.28 mmol/g, 0.054 mmol, 1 eq.). Subsequently, the resulting slurry was shaken for 1 day, the solution was drained, and the resin was washed with DCM x 2, DMF x 2 and DCM x 3. The dyed-pNO_2phenylglycolate test gave a pale red staining. (ca. 2-5% free amines). A second cycle with the same quantities was performed overnight, then the solution was drained and the resin washed with DCM (2 x 3 mL), DMF (2 x 3 mL) DCM (2 x 3 mL), DMF (2 x 3 mL) and DCM (3 x 3 mL) and dried in vacuo overnight (the dyed-pNO_2phenylglycolate test was negative after the second cycle), to get a resin type (q).

The resin was cleaved with 20% TFA in CH_2Cl_2 (2 times × 2.5 mL, 20 min), and crude compounds (XXVII-B-f) (32 mg) and (XXVII-B-h) (63 mg) were recovered after evaporation. The crude compounds were analyzed by TLC and ^1H NMR, and then purified by flash-chromatography.

8 mg of (XXVII-B-f) were obtained; yield over the six steps: 23%. 12 mg of (XXVII-B-h) were obtained; yield over the six steps: 20%.

(XXVII-B-f) - ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.88 (m, 3H, -$CH_2C\underline{H}_3$); 1.2-1.45 (m, 10H, -$COCH_2(C\underline{H}_2)_5CH_3$) 1.6-1.8 (m, 3H, $\underline{H}CH$ 1'+-$NHCOC\underline{H}_2$-); 2.3 (m, 1H, $HC\underline{H}$ 1'); 2.62 (m, 2H, $PhC\underline{H}_2CH_2$-); 2.92 (m, 2H, $PhCH_2C\underline{H}_2$-); 3.5-3.94 (m, 7H, H6+H5+H3+H2+H3'); 4.18 (m, 1H, H2'); 4.58 (m, 1H, H1); 4.64-4.82 (m, 4H, $PhC\underline{H}_2O$+ $PhC\underline{H}_2N$); 4.96 (dd, 1H, H4 J_1= 7.5 Hz J_2= 7.3 Hz); 7.08-7.4 (m, 15H, $\underline{Ar}$-).

(XXVII-B-h) - ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.8 (m, 1H, $\underline{H}CH$ 1'); 2.28 (m, 1H, $HC\underline{H}$ 1'); 2.6 (m, 2H, $PhC\underline{H}_2CH_2$-); 2.94 (m, 2H, $PhCH_2C\underline{H}_2$-); 3.5 (m, 2H, H3'); 3.7-4.0 (m, 9H, H6+H5+H3+-$O\underline{Me}$+-$NCOC\underline{H}_2Ar$); 4.12 (m, 1H, H2); 4.26 (m, 1H, H2');4.52-4.78 (m, 4H, $PhC\underline{H}_2O$+ p-MeO$PhC\underline{H}_2N$+H1); 4.97 (m, 1H, H4); 6.8-7.02 (m, 4H, p-MeO$\underline{Ph}CH_2N$-); 7.12-7.5 (m, 8H, $\underline{Ph}CH_2O$+Naphtyl); 7.8 (m,3H, Naphtyl). Mass spectrum (FAB^+) 730 (M^++1).

Example 35

By using anyone of the procedures above described in the previous examples with the proper intermediate derivatives, several other compounds have been prepared as per the following list, comprehensive of analytical data.

(XXVII-B-i) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-(isobutyrylamino)-3-O-propionyl-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =436.

(XXVII-B-j) 2,6:5,8-dianhydro-4-O-benzyl-3-O-(cyclopropylcarbonyl)-7,9-dideoxy-9-(isobutyrylamino)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =448.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,82 (m, 4H), 0,97 (m, 4H), 1,59 (m, 1H), 1,65 (m, 1H), 2,11 (m, 1H), 2,36 (m, 1H), 3,05-4,00 (bm, 8H), 4,50 (m, 1H), 4,60 (d, 1H, J=12), 4,69 (d, 1H, J=12), 4,85 (bs, 1H), 4,86 (m, 1H), 7,2-7,35 (m, 5H), 7,67 (bt, 1H).

(XXVII-B-k) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-(isobutyrylamino)-3-O-(pyridin-3-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =485.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0.96 (m, 6H), 1,72 (m, 1H), 2,17 (m, 1H), 2,34 (m, 1H), 3,2-4,0 (m, 8H), 4,57 (m, 1H), 4,61(d, 1H), 4,69 (d, 1H), 4,81 (bm, 1H), 5,15 (m, 1H), 7,16 (m, 5H), 7,56 (m, 1H), 7,69 (bm, 1H), 8,24 (m, 1H), 8,80 (m, 1H), 9,06 (s, 1H).

(XXVII-B-l) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-3-O-(4-fluorobenzoyl)-9-(isobutyrylamino)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =502.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,96 (m, 6H), 1,60 (m, 1H), 1,71 (m, 1H), 2,17 (m, 1H), 2,33 (m, 1H), 3,0-4,0 (bm, 8H), 4,55 (m, 1H), 4,60 (d, 1H), 4,70 (d, 1H), 4,80 (bs, 1H), 5,11 (m, 1H), 7,1-7,2 (m, 5H), 7,34 (t, 2H), 7,67 (bt, 1H), 8,00 (m, 2H).

(XXVII-B-m) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-(isobutyrylamino)-3-O-(thien-2-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =490.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,97 (t, 6H, J=6.8), 1,72 (m, 1H), 2,15 (m, 1H), 2,34 (m, 1H), 3,15-4,00 (m, 8H), 4,56 (m, 1H), 4,60 (d, 1H), 4,69 (d, 1H), 4,81 (bm, 1H), 5,06 (t, 1H, J=7.8), 7,2 (m, 6H), 7,66 (bt, 1H), 7,79 (m, 1H), 7,96 (m, 1H).

(XXVII-B-n) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-[(methoxyacetyl)amino]-3-O-(thien-2-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =492.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,72 (m, 1H), 2,20 (m, 1H), 3,15-4,00 (m, 11H), 4,51 (m, 1H), 4,63(d, 1H), 4,67 (d, 1H), 4,81 (bm, 1H), 5,06 (t, 1H, J=6.7), 7,22 (m, 6H), 7,67 (bt, 1H), 7,78 (m, 1H), 7,95 (m, 1H).

(XXVII-B-o) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-[(methoxyacetyl)amino]-3-O-(pyridin-3-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =487.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,72 (m, 1H), 2,23 (m, 1H), 3,4-4,0 (m, 10H), 4,51 (m, 1H), 4,64(d, 1H), 4,67 (d, 1H), 5,14 (m, 1H), 7,20 (m, 5H), 7,55 (m, 1H), 7,68 (bm, 1H), 8,23 (m, 1H), 8,81 (m, 1H), 9,06 (s, 1H).

(XXVII-B-p) 2,6:5,8-dianhydro-4-O-benzyl-3-O-(cyclopropylcarbonyl)-7,9-dideoxy-9-[(methoxyacetyl)amino]-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =450.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,87 (m, 4H), 1,59 (m, 1H), 2,17 (m, 1H), 2,36 (m, 1H), 3,05-3,8 (bm, 9H), 4,01 (m, 1H), 4,46 (m, 1H), 4,60 (d, 1H), 4,69 (d, 1H), 4,76 (bs, 1H), 4,86 (m, 1H), 7,2-7,4 (m, 5H), 7,66 (bt, 1H).

(XXVII-B-q) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-(N,N-dimethylglycylamino)-3-O-(pyridin-3-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =500.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,72 (m, 1H), 2,23 (m, 1H), 2,48 (m, 6H), 3,3-4,0 (m, 10H), 4,57 (m, 1H), 4,61(d, 1H), 4,69 (d, 1H), 4,81 (bm, 1H), 5,17 (m, 1H), 7,18 (m, 5H), 7,57 (m, 1H), 8,24 (m, 1H), 8,81 (m, 1H), 9,07 (s, 1H).

(XXVII-B-r) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-(N,N-dimethylglycylamino)-3-O-(thien-2-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =505.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,71 (m, 1H), 2,20 (m, 1H), 2,52 (s, 6H), 3,15-4,00 (m, 8H), 4,56 (m, 1H), 4,60 (d, 1H), 4,68 (d, 1H), 4,82 (bt, 1H), 5,08 (t, 1H, J=7.7), 7,2 (m, 6H), 7,79 (m, 1H), 7,95 (m, 1H).

(XXVII -B-s) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-(N,N-dimethylglycylamino)-3-O-4-(4-fluorobenzoyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =517.

(XXVII-C-f) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-3-O-(4-fluorobenzoyl)-9-{[(isopropylamino)carbonyl]amino}-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =517.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,00 (d, 6H, J=8.3), 1,73 (m, 1H), 2,16 (m, 1H), 3,62 (m, 3H), 3,82 (m, 4H), 4,54 (m, 1H), 4,60 (d, 1H), 4,69 (d, 1H), 4,79 (bm, 1H), 5,10 (m, 1H), 5,76 (m, 2H), 7,18 (m, 5H), 7,34 (m, 2H), 7,99 (m, 2H).

(XXVII-C-g) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-{[(isopropylamino)-carbonyl]amino}-3-O-propionyl-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =451

(XXVII-C-h) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-{[(isopropylamino)carbonyl]amino}-3-O-(pyridin-3-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =500

(XXVII-C-i) 2,6:5,8-dianhydro-4-O-benzyl-3-O-(cyclopropylcarbonyl)-7,9-dideoxy-9-{[(isopropylamino)carbonyl]amino}-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =464 .

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,82 (m, 4H), 1,0 (m, 6H), 1,59 (m, 2H), 2,10 (m, 1H), 3,1-3,8 (m, 9H), 4,52 (m, 1H), 4,60 (d, 1H), 4,69 (d, 1H), 4,75 (bs, 1H), 4,85 (m, 1H), 5,70 (bt, 1H), 5,57 (bm, 1H), 7,28 (m, 5H).

(XXVII-C-j) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-{[(isopropylamino)-carbonyl]amino}-3-O-(thien-2-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =505.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,00 (d, 6H, J=6.5), 1,68 (m, 1H), 2,14 (m, 1H), 3,29 (m, 2H), 3,6 (m, 3H), 3,84 (m, 4H), 4,58 (m, 1H), 4,62(d, 1H), 4,70 (d, 1H), 4,80 (bm, 1H), 5,05 (t, 1H, J=7.2), 5,75 (m, 2H), 7,19 (m, 6H), 7,79 (m, 1H), 7,95 (m, 1H).

(XXVII-C-l) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-3-O-(4-fluorobenzoyl)-9-({[(3-fluorophenyl)amino]carbonyl}amino)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =569.

(XXVII-C-m) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-({[(3-fluorophenyl)amino]carbonyl}amino)-3-O-propionyl-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =503.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,97 (t, 3H, J=5.5), 1,70 (m, 1H), 2,26 (m, 1H), 3,15-4,00 (m, 8H), 4,56 (m, 1H), 4,60 (d, 1H), 4,69 (d, 1H), 4,79 (bm, 1H), 4,86 (t, 1H, J=7.0), 6,30 (bt, 1H), 6,67 (m, 1H), 7,0-7,4 (m, 7H), 7,42 (m, 1H), 8,82 (bs, 1H).

(XXVII-C-n) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-({[(3-fluorophenyl)-amino]carbonyl}amino)-3-O-(pyridin-3-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =552.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,74 (m, 1H), 2,23 (m, 1H), 3,3-4,0 (m, 8H), 4,61 (m, 1H), 4,62(d, 1H), 4,71 (d, 1H), 4,81 (bm, 1H), 5,16 (m, 1H), 6,27 (m, 1H), 6,67 (m, 1H), 6,98 (m, 1H), 7,17 (m, 5H), 7,4-7,55 (m, 2H), 8,22 (m, 1H), 8,76 (m, 1H), 9,06 (s, 1H).

(XXVII-C-o) 2,6:5,8-dianhydro-4-O-benzyl-3-O-(cyclopropylcarbonyl)-7,9-dideoxy-9-({[(3-fluorophenyl)amino]carbonyl}amino)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =515.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,82 (m, 4H), 1,59 (m, 1H), 1,71 (m, 1H), 2,17 (m, 1H), 3,2-4,0 (bm, 8H), 4,52 (m, 1H), 4,60 (d, 1H), 4,70 (d, 1H), 4,76 (bs, 1H), 4,86 (m, 1H), 6,34 (bt, 1H), 6,66 (t, 1H), 7,2-7,4 (m, 7H), 7,42 (m, 1H), 7,66 (bt, 1H).

(XXVII-C-p) 2,6:5,8-dianhydro-4-O-benzyl-7,9-dideoxy-9-({[(3-fluorophenyl)-amino]carbonyl}amino)-3-O-(thien-2-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =557.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,73 (m, 1H), 2,20 (m, 1H), 3,2-4,0 (m, 8H), 4,57 (m, 1H), 4,62(d, 1H), 4,70 (d, 1H), 4,81 (bm, 1H), 5,06 (t, 1H, J=7.2), 6,26 (bt, 1H), 6,67 (m, 1H), 7,0 (d, 1H), 7,17 (m, 7H), 7,44 (m, 1H), 7,79 (m, 1H), 7,92 (m, 1H), 8,77 (bs, 1H).

(XXVII-C-q) 2,6:5,8-dianhydro-4-O-benzyl-7,9-didcoxy-3-O-(4-fluorobenzoyl)-9-({[(3-methoxyphenyl)amino]carbonyl}amino)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =581 .

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,73 (m, 1H), 2,20 (m, 1H), 3,1-4,1 (bm, 11H), 4,56 (m, 1H), 4,60 (d, 1H), 4,69 (d, 1H), 4,80 (bm, 1H), 5,11 (m, 1H), 6,20 (bt, 1H), 6.46 (m, 1H), 6,6-7,35 (m, 10H), 7,99 (m, 2H), 8,53 (s, 1H).

(XXVII-C-r) 2,6:5,8-dianhydro-4-O-benzyl-3-O-(cyclopropylcarbonyl)-7,9-dideoxy-9-({[(3-methoxyphenyl)amino]carbonyl}amino)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =527 .

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 0,82 (m, 4H), 1,59 (m, 1H), 1,71 (m, 1H), 2,16 (m, 1H), 3,2-4,0 (bm, 10H), 4,52 (m, 1H), 4,60 (d, 1H), 4,70 (d, 1H), 4,76 (bs, 1H), 4,86 (m, 1H), 6,18 (bt, 1H), 6,45 (m, 1H), 6,82 (m, 1H), 7,05-7,3 (m, 7H), 8,54 (bt, 1H).

(XXVII-C-s) 2,6:5,8-dianhydro-4-O-benzyl-7,9-didcoxy-9-({[(3-methoxyphenyl)amino]carbonyl}amino)-3-O-(thien-2-ylcarbonyl)-D-glycero-L-gulo-nonitol

MS : $[M+H]^+$ =569.

^{1}H-NMR (DMSO-d_6), diagnostic signals, δ (ppm): 1,73 (m, 1H), 2,19 (m, 1H), 3,67 (s, 3H), 3,8-4,1 (m, 4H), 4,57 (m, 1H), 4,62(d, 1H), 4,70 (d, 1H), 4,81 (bm, 1H), 5,06 (t, 1H, J=7.1), 6,19 (m, 1H), 6,46 (bt, 1H), 6,84 (m, 1H), 7,12 (m, 7H), 7,78 (m, 1H), 7,93 (m, 1H), 8,55 (bs, 1H).